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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Judi BRYANT et alf.

Serial No. : 10/722,591

Filed : November 28, 2003

For : CHK-, PDK- AND AKT-INHIBITORY PYRIMIDINES, THEIR PRODUCTION AND USE AS PHARMACEUTICAL AGENTS

SUBMISSION OF PRIORITY DOCUMENT(S)

Commissioner for Patents
P.O. Box 1450
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Sir:

Submitted herewith is a certified copy of each of the below-identified document(s), benefit of priority of each of which is claimed under 35 U.S.C. § 119:

COUNTRY	APPLICATION NO.	FILING DATE
Germany	02026607.8	November 28, 2002

Acknowledgment of the receipt of the above document(s) is requested.

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Respectfully submitted,

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Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02026607.8

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Chk-, pdk- and akt-inhibitory pyrimidines, their production and use as pharmaceutical agents

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Chk-, Pdk- and Akt-Inhibitory Pyrimidines, Their Production and Use as Pharmaceutical Agents

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Chk-, Pdk- and Akt-Inhibitory Pyrimidines, Their Production and Use as Pharmaceutical Agents

Description

This invention relates to pyrimidine derivatives, their production as well as their use as medications for treating various diseases.

The Chks (checkpoint kinases)-, Akts (protein kinases B) and Pdks (phosphoinositide-dependent kinases) are enzyme families that play an important role in the regulation of the cell cycle and thus is an especially advantageous target for the development of small inhibitory molecules. Akts and Pdks may be involved in common signal transduction pathways. Selective inhibitors of the Chks and Akts and/or Pdks, particularly of Pdk1 can be used for treating cancer or other diseases that cause disruptions of cell proliferation.

Pyrimidines and analogs are already described as active ingredients, such as, for example, the 2-anilino-pyrimidines as fungicides (DE-A-4029650) or substituted pyrimidine derivatives for treating neurological or neurodegenerative diseases (WO 99/19305). As CDK-inhibitors, the most varied pyrimidine derivatives are described, for example bis(anilino)-pyrimidine derivatives (WO 00/12486), 2-amino-4-substituted pyrimidines (WO 01/14375), purines (WO 99/02162), 5-cyano-pyrimidines (WO 02/04429), anilinopyrimidines (WO 00/12486) and 2-hydroxy-3-N,N-dimethylaminopropoxy-pyrimidines (WO 00/39101).

The object of this invention is to provide compounds that have better properties than the inhibitors that are already known. The substances that are described here are more effective, since they already inhibit in the

nanomolar range and can be distinguished from other already known Cdk-inhibitors such as, e.g., olomoucine and roscovitine.

It has now been found that the novel compounds of general formulae I, II, III and IV as well as isomers, diastereomers, enantiomers and salts thereof are capable of inhibiting kinases which are involved in the regulation of the cell cycle, particularly Chks, Akt, Pdks and/or Cdks. Preferably, the compounds are capable of inhibiting the activity of Chks, Akts and/or Pdks. Thus, the novel compounds as defined in the claims may be used for the manufacture of pharmaceutical compositions and medicaments, which are suitable for the prevention or treatment of disorders caused by, associated with or accompanied by disruptions of cell proliferation. More particularly, the compounds of the present invention are suitable for the prevention or treatment of hyperproliferative disorders caused by, associated with or accompanied by an abnormal activity, e.g. an abnormally increased activity of kinases as recited above.

Further, it has been found that compounds of the general formulae V, VI and VII are capable of inhibiting the activity of kinases selected from Chk, Akt and/or Pdk. Thus, these compounds are suitable for the manufacture of a medicament for the prevention or treatment of a disorder caused by, associated with or accompanied by by an abnormal kinase activity, e.g. an abnormally increased kinase activity selected from Chk, Akt and/or Pdk activity.

Preferred aspects of the present invention are described in the claims. A more detailed explanation of the terms used in the claims is given in the following:

Alkyl is defined in each case as a straight-chain or branched alkyl radical, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl, octyl, nonyl and decyl.

Alkoxy is defined in each case as a straight-chain or branched alkoxy radical, such as, for example, methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy, pentyloxy, isopentyloxy, or hexyloxy.

Alkylthio is defined in each case as a straight-chain or branched alkylthio radical, such as, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, isopentylthio or hexylthio.

Cycloalkyl is defined in general as monocyclic alkyl rings, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, but also bicyclic rings or tricyclic rings such as, for example, norbornyl, adamantanyl, etc.

The ring systems, in which optionally one or more possible double bonds can be contained in the ring, are defined as, for example, cycloalkenyls, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, or cycloheptenyl, whereby the linkage can be carried out both to the double bond and to the single bonds.

If A and B, R^3 and R^4, X and R^2 as defined in the claims, in each case independently of one another, together form a C_3-C_{10}-cycloalkyl ring, which optionally can be interrupted by one or more heteroatoms, such as nitrogen atoms, oxygen atoms and/or sulfur atoms, and/or can be interrupted by one or more $=C=O$ groups in the ring and/or optionally one or more possible double bonds can be contained in the ring, however, the above-mentioned definitions are also intended to include heteroaryl radical or heterocycloalkyl and heterocycloalkenyl.

Halogen is defined in each case as fluorine, chlorine, bromine or iodine.

The alkenyl substituents in each case are straight-chain or branched, whereby, for example, the following radicals are meant: vinyl, propen-1-yl, propen-2-yl, but-1-en-1-yl, but-1-en-2-yl, but-2-en-1-yl, but-2-en-2-yl, 2-methyl-prop-2-en-1-yl, 2-methyl-prop-1-en-1-yl, but-1-en-3-yl, ethinyl, prop-1-in-1-yl, but-1-in-1-yl, but-2-in-1-yl, but-3-en-1-yl, and allyl.

Alkinyl is defined in each case as a straight-chain or branched alkinyl radical that contains 2-6, preferably 2-4 C atoms. For example, the following radicals can be mentioned: acetylene, propin-1-yl, propin-3-yl, but-1-in-1-yl, but-1-in-4-yl, but-2-in-1-yl, but-1-in-3-yl, etc.

The aryl radical in each case comprises 3-16 carbon atoms and in each case can be benzocondensed.

For example, there can be mentioned: cyclopropenyl, cyclopentadienyl, phenyl, tropyl, cyclooctadienyl, indenyl, naphthyl, azulenyl, biphenyl, fluorenyl, anthracenyl, etc.

The heteroaryl radical in each case comprises 3-16 ring atoms, and instead of the carbon can contain one or more heteroatoms that are the same or different, such as oxygen, nitrogen or sulfur, in the ring, and can be monocyclic, bicyclic, or tricyclic and in addition in each case can be benzocondensed.

For example, there can be mentioned:

Thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, etc. and benzo derivatives thereof, such as, e.g., benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, indazolyl, indolyl, isoindolyl, etc.; or pyridyl,

pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, etc. and benzo derivatives thereof, such as, e.g., quinolyl, isoquinolyl, etc., or azocinyl, indolizinyl, purinyl, etc. and benzo derivatives thereof; or quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, oxepinyl, etc.

Heterocycloalkyl stands for an alkyl ring that comprises 3-12 carbon atoms, which instead of the carbon contains one or more heteroatoms that are the same or different, such as, e.g., oxygen, sulfur or nitrogen.

As heterocycloalkyls, there can be mentioned, e.g.: oxiranyl, oxethanyl, aziridinyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, imidazolidinyl, pyrazolidinyl, dioxanyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, trithianyl, quinuclidinyl, etc.

Heterocycloalkenyl stands for an alkyl ring that comprises 3-12 carbon atoms, which instead of the carbon contains one or more heteroatoms that are the same or different such as, e.g., oxygen, sulfur or nitrogen, and which is partially saturated.

As heterocycloalkenyls, there can be mentioned, e.g.: pyran, thiin, dihydroacet, etc.

If an acid group is included, the physiologically compatible salts of organic and inorganic bases are suitable as salts, such as, for example, the readily soluble alkali and alkaline-earth salts, as well as N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, 1,6-hexadiamine, ethanolamine, glucosamine, sarcosine, serinol, tris-hydroxy-methyl-aminomethane, aminopropane diol, Sovak base, and 1-amino-2,3,4-butanetriol.

If a basic group is included, the physiologically compatible salts of organic and inorganic acids are suitable, such as hydrochloric acid, sulfuric acid, phosphoric acid, citric acid, tartaric acid.

The compounds according to the invention essentially inhibit cell-cycle-associated kinases, particularly serin/threonine kinases, more particularly cyclin-dependent kinases (Cdks), Chks, Akts and/or Pdks. Especially preferred is the inhibition of Chks, e.g. Chk1 and/or Chk2, Akts, e.g. Akt1, Akt2 and/or Akt3 and/or Pdks, e.g. Pdk1. Of particular interest is a selective inhibition of specific kinases. For example, the compounds of formulae (III) or (VII) show a selectivity towards Chks, e.g. Chk1 and/or Chk2 and the compounds of formulae (IV) or (VI) show a selectivity toward Akts, e.g. Akt1, Akt2 and/or Akt3 and/or Pdks, e.g. Pdk1 upon which is based their action, for example, against cancer, such as solid tumors and leukemia; auto-immune diseases such as psoriasis, alopecia, and multiple sclerosis, chemotherapy-induced alopecia and mucositis; cardiovascular diseases such as stenoses, arterioscleroses and restenoses; infectious diseases, such as, e.g., by unicellular parasites, such as trypanosoma, toxoplasma or plasmodium, or produced by fungi; nephrological diseases, such as, e.g., glomerulonephritis, chronic neurodegenerative diseases, such as Huntington's disease, amyotropic lateral sclerosis, Parkinson's disease, AIDS dementia and Alzheimer's disease; acute neurodegenerative diseases, such as ischemias of the brain and neurotraumas; viral infections, such as, e.g., cytomegalic infections, herpes, Hepatitis B and C, and HIV diseases.

The eukaryotic cell division ensures the duplication of the genome and its distribution to the daughter cells by passing through a coordinated and regulated sequence of events. The cell cycle is divided into four successive phases: the G1 phase represents the time before the DNA replication, in which the cell grows and is sensitive to external stimuli. In

the S phase, the cell replicates its DNA, and in the G2 phase, preparations are made for entry into mitosis. In mitosis (M phase), the replicated DNA separates, and cell division is completed.

The loss of the regulation of the cell cycle and the loss of function of the control points are characteristics of tumor cells.

Changes of the cell cycle control play a role not only in carcinoses. The cell cycle is activated by a number of viruses, both by transforming viruses as well as by non-transforming viruses, to make possible the replication of viruses in the host cell. The false entry into the cell cycle of normally post-mitotic cells is associated with various neurodegenerative diseases. The mechanisms of the cell cycle regulation, their changes in diseases and a number of approaches to develop inhibitors of the cell cycle progression and especially the CDKs were already described in a detailed summary in several publications (Sielecki, T. M. et al. (2000). Cyclin-Dependent Kinase Inhibitors: Useful Targets in Cell Cycle Regulation. J. Med. Chem. 43, 1-18; Fry, D. W. & Garrett, M. D. (2000). Inhibitors of Cyclin-Dependent Kinases as Therapeutic Agents for the Treatment of Cancer. Curr. Opin. Oncol. Endo. Metab. Invest. Drugs 2, 40-59; Rosiania, G. R. & Chang, Y. T. (2000). Targeting Hyperproliferative Disorders with Cyclin-Dependent Kinase Inhibitors. Exp. Opin. Ther. Patents 10, 215-230; Meijer L. et al. (1999). Properties and Potential Applications of Chemical Inhibitors of Cyclin-Dependent Kinases. Pharmacol. Ther. 82, 279-284; Senderowicz, A. M. & Sausville, E. A. (2000). Preclinical and Clinical Development of Cyclin-Dependent Kinase Modulators. J. Natl. Cancer Inst. 92, 376-387).

To use the compounds according to the invention as pharmaceutical agents, the latter are brought into the form of a pharmaceutical preparation, which in addition to the active ingredient for enteral or parenteral administration contains suitable pharmaceutical, organic or

inorganic inert carrier materials, such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc. The pharmaceutical preparations can be present in solid form, for example as tablets, coated tablets, suppositories, or capsules, or in liquid form, for example as solutions, suspensions, or emulsions. Moreover, they optionally contain adjuvants, such as preservatives, stabilizers, wetting agents or emulsifiers; salts for changing the osmotic pressure or buffers. These pharmaceutical preparations are also subjects of this invention.

For parenteral administration, especially injection solutions or suspensions, especially aqueous solutions of active compounds in polyhydroxy-ethoxylated castor oil, are suitable.

As carrier systems, surface-active adjuvants such as salts of bile acids or animal or plant phospholipids, but also mixtures thereof , as well as liposomes or their components can also be used.

For oral administration, especially tablets, coated tablets or capsules with talc and/or hydrocarbon vehicles or binders, such as, for example, lactose, corn or potato starch, are suitable. The administration can also be carried out in liquid form, such as, for example, as a juice, to which optionally a sweetener is added.

Enteral, parenteral and oral administrations are also subjects of this invention. The dosage of the active ingredients can vary depending on the method of administration, age and weight of the patient, type and severity of the disease to be treated and similar factors. The daily dose is 0.5-1000 mg, preferably 50-200 mg, whereby the dose can be given as a single dose to be administered once or divided into two or more daily doses.

Subjects of this invention also include the use of compounds of general formulae I-VII for the production of a pharmaceutical agent for treating cancer, auto-immune diseases, cardiovascular diseases, chemotherapy agent-induced alopecia and mucositis, infectious diseases, nephrological diseases, chronic and acute neurodegenerative diseases and viral infections, whereby cancer is defined as solid tumors and leukemia; auto-immune diseases are defined as psoriasis, alopecia and multiple sclerosis; cardiovascular diseases are defined as stenoses, arterioscleroses and restenoses; infectious diseases are defined as diseases that are caused by unicellular parasites; nephrological diseases are defined as glomerulonephritis; chronic neurodegenerative diseases are defined as Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease, AIDS dementia and Alzheimer's disease; acute neurodegenerative diseases are defined as ischemias of the brain and neurotraumas; and viral infections are defined as cytomegalic infections, herpes, hepatitis B or C, and HIV diseases.

Particularly, the compounds of the invention are suitable for the prevention or treatment of diseases, which are associated with or accompanied by an abnormal kinase activity, e.g. an abnormally increased kinase activity, preferably selected from Chk, Akt, Pdk and/or Cdk activity, more preferably selected from Chk, Akt and/or Pdk activity. The presence of an abnormally increased kinase activity in a patient can be determined by standard assays, e.g. as described in the Examples. Subjects of this invention also include pharmaceutical agents for treating the above-cited diseases, which contain at least one compound according to general formulae I-VII, as well as pharmaceutical agents with suitable formulation substances and vehicles.

If the production of the starting compounds for the manufacture of the compounds of the invention is not described, these starting compounds are known or can be produced analogously to known compounds or to

processes that are described here. It is also possible to perform all reactions that are described here in parallel reactors or by means of combinatory operating procedures.

The isomer mixtures can be separated into the enantiomers or E/Z isomers according to commonly used methods, such as, for example, crystallization, chromatography or salt formation.

The production of the salts is carried out in the usual way by a solution of the compound of formulae I-VII being mixed with the equivalent amount of or excess base or acid, which optionally is in solution, and the precipitate being separated or the solution being worked up in the usual way.

Further, the invention is explained in more detail by the enclosed drawings and examples.

Figure 1 shows five reaction schemes, which are suitable for the manufacture of compounds according to the present invention.

Figures 2-3 show compounds which inhibit Akt/Pdk activity.

Figures 4-9 show compounds which inhibit Chk activity.

Examples

A. Synthesis of Compounds

A1.

5-Bromo-4-(2-(1H-imidazol-4-yl)-ethylamino)-2-(4-pyrrolidin-1-ylmethyl-phenylamino)-pyrimidine

1a) 5-Bromo-2,4-dichloropyrimidine

To 5-bromouracil (50 g) were sequentially added N,N-diethylaniline (60 mL) and phosphoryl chloride (120 mL), and the mixture was refluxed for 5 h. The volatiles were removed by distillation, the residue poured into ice water and the mixture extracted with methyl tert-butyl ether. The combined extracts were washed with brine, dried (Na_2SO_4) and filtered through Celite. Distillation of the crude product gave the title compound (63.4 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 8.69 (s, 1H).

1b) 5-Bromo-4-(2-(1H-imidazol-4-yl)-ethylamino)-2-chloro-pyrimidine

To a solution of 5-bromo-2,4-dichloropyrimidine (4.56 g) and triethylamine (3 mL) in acetonitrile (20 mL) 2-(1H-imidazol-4-yl)-ethylamine (2.45 g) was added portionwise at 0°C, and the suspension stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and brine, the aqueous phase extracted with additional ethyl acetate, the combined organic phases dried (Na_2SO_4) and evaporated, which gave, after chromatography on silica using dichloromethane/methanol, the title compound (4.41 g).

^{1}H NMR (300 MHz, CD_3OD): δ/ppm = 2.91 (t, 2H, J = 7 Hz), 3.73 (t, 2H, J = 7 Hz), 6.87 (s, 1H), 7.61 (s, 1H), 8.11 (s, 1H).

1c) 4-Pyrrolidin-1-ylmethyl-phenylamine

To a suspension of sodium hydride (60% in oil, 220 mg) in THF (5 mL) pyrrolidine (391 mg) was added, the mixture stirred at r.t. for 6 h, a solution of 1-bromomethyl-4-nitro-benzene (1.08 g) in THF (8 mL) added and stirred overnight. The reaction was quenched with water and extracted

with ethyl acetate, the organic phase dried (Na_2SO_4) and evaporated, which gave, after chromatography on silica using dichloromethane/methanol, 1-(4-nitro-benzyl)-pyrrolidine (690 mg).

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 1.84 (m, 4H), 2.58 (m, 4H), 3.77 (s, 2H), 7.61 (dbr, 2H, J = 9 Hz), 8.22 (dbr, 2H, J = 9 Hz).

To a solution of 1-(4-nitro-benzyl)-pyrrolidine (1.37 g) in ethanol (66 mL) tin(II)-chloride dihydrate (9.0 g) was added portionwise and the resulting mixture refluxed for 2 h. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution, the aqueous phase extracted with additional ethyl acetate, the combined organic phases dried (Na_2SO_4) and evaporated, which gave, after chromatography on silica using dichloromethane/methanol, the title compound (432 mg).

^{1}H NMR (300 MHz, CD_3OD): δ/ppm = 1.85 (m, 4H), 2.65 (m, 4H), 3.61 (s, 2H), 6.72 (d, 2H, J = 9 Hz), 7.11 (d, 2H, J = 9 Hz).

1d) 5-Bromo-4-(2-(1H-imidazol-4-yl)-ethylamino)-2-(4-pyrrolidin-1-ylmethyl-phenylamino)-pyrimidine

A mixture of 5-bromo-4-(2-(1H-imidazol-4-yl)-ethylamino)-2-chloro-pyrimidine (60 mg), 4-pyrrolidin-1-ylmethyl-phenylamine (35 mg) and hydrochloric acid (37% in water, 40 μL) in methanol (2 mL) was refluxed overnight. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution, the organic phase dried (Na_2SO_4) and evaporated, which gave, after chromatography on silica using dichloromethane/methanol, the title compound (4 mg).

^{1}H NMR (400 MHz, CD_3OD): δ/ppm = 2.09 (m, 4H), 3.02 (t, 2H, J = 7 Hz), 3.31 (m, 4H), 3.79 (t, 2H, J = 7 Hz), 4.30 (s, 2H), 7.11 (s, 1H), 7.40 (d, 2H, J = 9 Hz), 7.76 (d, 2H, J = 9 Hz), 7.97 (s, 1H), 8.19 (s, 1H).

A2

2-(4-(Aminomethyl)-phenylamino)-4-(prop-2-ynylamino)-5-trifluoromethyl-pyrimidine

2a) 2,4-Dichloro-5-trifluoromethyl-pyrimidine

To 5-trifluoromethyluracil (25 g) were sequentially added N,N-diethylaniline (25 g) and phosphoryl chloride (94 g), and the mixture was refluxed for 18 h. After cooling to r.t. the solution was poured onto ice (100 g), stirred for 10 min. and extracted with diethyl ether. The combined organic phases were washed with saturated aqueous sodium carbonate solution and water, dried (Na_2SO_4), and filtered. After removal of most of the ether, distillation of the residue at 190°C and 860 to 300 mbar gave the title compound (5.8 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 8.83 (s, 1H).

2b) 2-Chloro-4-(prop-2-ynylamino)-5-trifluoromethyl-pyrimidine

To a solution of 2,4-dichloro-5-trifluoromethyl-pyrimidine (3.47 g) in acetonitrile (16 mL) a solution of propargylamine (1.76 g) in acetonitrile (16 mL) was added dropwise at 0°C, the mixture warmed to r.t. and stirred at r.t. for 48 h. The suspension was diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography on silica using hexane/methyl tert-butyl ether gave the title compound (1.97 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 2.34 (t, 1H, J = 1.5 Hz), 4.37 (dd, 2H, J = 1.5/5 Hz), 5.53 (brs, 1H), 8.33 (s, 1H).

2c) 2-(4-(Aminomethyl)-phenylamino)-4-(prop-2-ynylamino)-5-trifluoro-methyl-pyrimidine

A mixture of 2-chloro-4-(prop-2-ynylamino)-5-trifluoromethyl-pyrimidine (235 mg), N-(4-aminobenzyl)-2,2,2-trifluoro-acetamide (410 mg) and hydrochloric acid (37% in water, 0.2 mL) in methanol (5 mL) was refluxed for 1 h. The reaction mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution, the aqueous phase extracted with ethyl acetate, the combined organic phases dried (Na_2SO_4), concentrated, filtered through silica using dichloromethane/methanol, and the filtrate evaporated. To a solution of the residue in methanol (9 mL), tetrahydrofuran (9 mL) and diethyl ether (4.5 mL) was added lithium hydroxide (150 mg) and the mixture was refluxed for 6 h, after which it was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with additional ethyl acetate, the combined organic phases dried (Na_2SO_4) and evaporated, which gave, after chromatography on silica using dichloromethane/ methanol, the title compound (120 mg).

^{1}H NMR (300 MHz, CD_3OD): δ/ppm = 2.55 (t, 1H, J = 1.5 Hz), 4.07 (s, 2H), 4.26 (d, 2H, J = 1.5 Hz), 7.39 (d, 2H, J = 8 Hz), 7.86 (d, 2H, J = 8 Hz).

A3

(2S)-1-(3-(5-Bromo-4-prop-2-ynyloxy-pyrimidin-2-ylamino)-phenoxy)-3-(4-methyl-piperazin-1-yl)-propan-2-ol

3a) 5-Bromo-2-chloro-4-prop-2-ynyloxy-pyrimidine

A mixture of 5-bromo-2,4-dichloropyrimidine (10 g), propargyl alcohol (11.5 mL) and trifluoromethanesulfonic acid (2.3 mL) was stirred at r.t. overnight and evaporated to dryness. Purification by flash chromatography on silica using toluene/methylene chloride gave the title compound (5.8 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 2.58 (t, 1H, J = 2.5 Hz), 5.09 (d, 2H, J = 2.5 Hz), 8.48 (s, 1H).

3b) 3-(5-Bromo-4-prop-2-ynyloxy-pyrimidin-2-ylamino)-phenol

5-Bromo-2-chloro-4-(prop-2-ynyloxy)-pyrimidine (26.5 g) and 3-aminophenol (23.3 g) were dissolved in tetrahydrofuran (190 mL) and water (90 mL), and the mixture was refluxed for 24 h. Evaporation to dryness followed by flash chromatography on silica using hexane/ethyl acetate gave the title compound (26.7 g).

^{1}H NMR (300 MHz, DMSO-d_6): δ/ppm = 3.66 (t, 1H, J = 1.5 Hz), 5.12 (d, 2H, J = 1.5 Hz), 6.39 (dbr, J = 8 Hz), 7.05 (t, 1H, J = 8 Hz), 7.15 (d, 1H, J = 8 Hz), 7.22 (sbr, 1H), 8.40 (s, 1H), 9.32 (s, 1H), 9.70 (s, 1H).

3c) (2S)-(5-Bromo-4-prop-2-ynyloxy-pyrimidin-2-yl)-(3-oxiranylmethoxy-phenyl)-amine

A mixture of sodium hydride (60% in oil, 2.0 g) and 3-(5-bromo-4-prop-2-ynyloxy-pyrimidin-2-ylamino)-phenol (12.9 g) in THF (80 mL) was stirred at r.t. for 30 min., a solution of (2S)-glycidyl tosylate (9.1 g) in DMF (40 mL) added, and stirring continued for 20 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and evaporated, which gave, after chromatography on silica using dichloromethane/ethyl acetate, the title compound (4.24 g).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 2.71 (dd, 1H, J = 2.5/5 Hz), 2.85 (t, 1H, J = 5 Hz), 3.62 (t, 1H, J = 1.5 Hz), 3.82 (dd, 1H, J = 6/11 Hz), 4.31 (dd, 1H, J = 2.5/11 Hz), 5.12 (d, 2H, J = 1.5 Hz), 6.59 (dbr, 1H, J = 8.5 Hz), 7.19 (t, 1H, J = 8.5 Hz), 7.31 (d, 1H, J = 8.5 Hz), 7.44 (s, 1H), 8.43 (s, 1H), 9.78 (s, 1H).

3d) (2S)-1-(3-(5-Bromo-4-prop-2-ynyloxy-pyrimidin-2-ylamino)-phenoxy)-3-(4-methyl-piperazin-1-yl)-propan-2-ol

To a suspension of (2S)-(5-bromo-4-prop-2-ynyloxy-pyrimidin-2-yl)-(3-oxiranyl-methoxyphenyl)-amine (188 mg) in ethanol (1.3 mL) a solution of N-methylpiperazine (111 μL) in ethanol (1.3 mL) was added an the mixture stirred at 80°C for 8 h. The solution was partioned between ethyl acetate and water, and the organic phase evaporated, which gave, after chromatography on silica using dichloromethane/methanol, the title compound (37 mg).

^{1}H NMR (300 MHz, DMSO-d_6): δ/ppm = 2.08 (s, 1H), 2.13 (s, 3H), 2.27-2.49 (m, 9H), 3.66 (t, 1H, J = 2.5 Hz), 3.79-3.99 (m, 3H), 4.82 (m, 1H), 5.12 (d, 2H, J = 2.5 Hz), 6.56 (dd, 1H, J = 2/8 Hz), 7.17 (t, 1H, J = 8 Hz), 7.28 (dbr, 1H, J = 8 Hz), 7.41 (t, 1H, J = 2 Hz), 8.43 (s, 1H). 9.79 (s, 1H).

A4

N-(3-((2-((4-(aminosulfonyl)phenyl)amino)-5-bromo-4-pyrimidinyl)amino) propyl)-1H-pyrrole-2-carboxamide

4a) (3-((5-bromo-2-chloro-4-pyrimidinyl)amino)propyl)-carbamic acid tert-butyl ester

To a solution of 5-bromo-2,4-dichloro-pyrimidine (1.4 g) in acetonitrile (10 mL) at 0°C was added triethylamine (0.94 mL) and 3-aminopropylcarbamic acid-1,1-dimethylethyl ester (1.0 g). After removing the cooling bath the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated and to the residue water (20 mL) was added. The precipitate was collected, washed with water and ether to afford the title compound (1.8 g).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 1.34 (s, 9H), 1.62 (m, 2H), 2.93 (m, 2H), 3.36 (m, 2H), 6.78 (t, 1H), 7.64 (t, 1H), 8.22 (s, 1H).

4b) 4-((4-((3-aminopropyl)amino)-5-bromo-2-pyrimidinyl)amino)-benzene-sulfonamide hydrochloride

To a solution of 4-aminobenzenesulfonamide (190 mg) in acetonitrile (20 mL), hydrochloric acid solution (4M in dioxane, 0.3 mL) and water (0.3 mL) was added (3-((5-bromo-2-chloro-4-pyrimidinyl)amino)propyl)-carbamic acid-1,1-dimethylethyl ester (360 mg). The resulting mixture was refluxed overnight. The precipitate was collected and washed with acetonitrile and methanol to afford the title compound (320 mg).

1H NMR (400 MHz, DMSO-d6): d/ppm = 1.86 (m, 2H), 2.78 (m, 2H), 3.51 (m, 2H), 7.23 (s, 2H), 7.75 (d, 2H), 7.79 (d, 2H), 7.96 (m, 3H), 8.19 (s, 1H), 10.38 (t, 1H).

4c) N-(3-((2-((4-(aminosulfonyl)phenyl)amino)-5-bromo-4-pyrimidinyl) amino)propyl)-1H-pyrrole-2-carboxamide trifluoroacetate

4-((4-((3-aminopropyl)amino)-5-bromo-2-pyrimidinyl)amino)-benzenesulfonamide (120 mg) was suspended in dimethylformamide (5 mL). 2-Pyrrolecarboxylic acid (50 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (180 mg), and diisopropylethylamine (0.3 mL) were added and the resulting mixture was stirred at room temperature for 15 min. Purification by HPLC chromatography using acetonitrile/water gave the title compound (65 mg).

^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 1.78 (m, 2H), 3.27 (m, 2H), 3.44 (m, 2H), 6.03 (d, 1H), 6.71 (s, 1H), 6.80 (s, 1H), 7.14 (s, 2H), 7.42 (t, 1H), 7.68 (d, 2H), 7.83 (d, 2H), 8.04 (t, 1H), 8.11 (s, 1H), 9.78 (s, 1H), 11.39 (s, 1H).

The following examples were prepared in analogy to the examples described above.

Example	Compound	Supporting Data
5	*N2*-(4-(2-aminoethyl)phenyl)-*N4*-2-propynyl-5-(trifluoromethyl)-2,4-pyrimidinediamine	336 (ESI-MS)
6	5-bromo-2-((4-(2-hydroxyethyl)phenyl)amino)-4-pyrimidinol	311 (ESI-MS)
7	2-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-benzeneethanol	349 (ESI-MS)
8	3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-benzoic acid ethyl ester	377 (ESI-MS)
9	3-((5-bromo-4-ethoxy-2-pyrimidinyl)amino)-benzoic acid ethyl ester	367 (ESI-MS)
10	4-((5-bromo-4-ethoxy-2-pyrimidinyl)amino)-benzoic acid ethyl ester	367 (ESI-MS)
11	4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-benzeneethanol	349 (ESI-MS)
12	4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-benzoic acid ethyl ester	377 (ESI-MS)
13	2-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-benzoic acid ethyl ester	377 (ESI-MS)
14	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2-pyridinyl)-1-piperazineethanol	540 (ESI-MS)

15	4-(1,3-benzodioxol-5-ylmethyl)-α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-phenoxy)methyl)-1-piperazineethanol	597 (ESI-MS)
16	4-(bis(4-fluorophenyl)methyl)-α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-phenoxy)methyl)-1-piperazineethanol	665 (ESI-MS)
17	2-(4-(3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)-1-piperazinyl)-benzonitrile	564 (ESI-MS)
18	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2,4-dimethoxyphenyl)-1-piperazineethanol	599 (ESI-MS)
19	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2-ethoxyethyl)-1-piperazineethanol	535 (ESI-MS)
20	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-pyrrolidineethanol	448 (ESI-MS)
21	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-morpholineethanol	464 (ESI-MS)
22	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-thiomorpholineethanol	480 (ESI-MS)
23	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2-pyridinyl)-1-piperazineethanol	540 (ESI-MS)
24	4-(1,3-benzodioxol-5-ylmethyl)-α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)-phenoxy)methyl)-1-piperazineethanol	597 (ESI-MS)
25	4-(bis(4-fluorophenyl)methyl)-α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-methyl)-1-piperazineethanol	665 (ESI-MS)
26	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-pyrazinyl-1-piperazineethanol	541 (ESI-MS)
27	2-(4-(3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)-1-piperazinyl)-benzonitrile	564 (ESI-MS)
28	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2,4-dimethoxyphenyl)-1-piperazineethanol	599 (ESI-MS)
29	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-((tetrahydro-2-furanyl)carbonyl)-1-piperazineethanol	561 (ESI-MS)
30	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-morpholineethanol	464 (ESI-MS)
31	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(phenylmethyl)-1-piperidineethanol	552 (ESI-MS)

32	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-2-(((2,6-dimethylphenyl)amino)methyl)-1-pyrrolidineethanol	581 (ESI-MS)
33	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-(2-thienyl)ethyl)amino)-2-propanol	504 (ESI-MS)
34	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((1,2,3,4-tetrahydro-1-naphthalenyl)amino)-2-propanol	524 (ESI-MS)
35	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(3-(trifluoromethyl)phenyl)-1-piperazineethanol	607 (ESI-MS)
36	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2-fluorophenyl)-1-piperazineethanol	557 (ESI-MS)
37	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(3-methoxyphenyl)-1-piperazineethanol	569 (ESI-MS)
38	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2-phenylethyl)-1-piperazineethanol	567 (ESI-MS)
39	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(2-furanylcarbonyl)-1-piperazineethanol	557 (ESI-MS)
40	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)hexahydro-4-(phenylmethyl)-*1H*-1,4-diazepine-1-ethanol	567 (ESI-MS)
41	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1,4-dioxa-8-azaspiro(4.5)decane-8-ethanol	520 (ESI-MS)
42	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((3-phenylpropyl)amino)-2-propanol	512 (ESI-MS)
43	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-phenyl-1-piperazineethanol	539 (ESI-MS)
44	4-((5-bromo-4-ethoxy-2-pyrimidinyl)amino)-benzeneethanol	339 (ESI-MS)
45	*N*-(4-((5-bromo-4-(2-propynylamino)-2-pyrimidinyl)amino)phenyl)-acetamide	361 (ESI-MS)
46	*N*-(4-((5-bromo-4-(2-propynylamino)-2-pyrimidinyl)amino)phenyl)-2,2,2-trifluoro-acetamide	415 (ESI-MS)
47	*N2*-(4-aminophenyl)-5-bromo-*N4*-2-propynyl-2,4-pyrimidinediamine	319 (ESI-MS)
48	*N*-((4-((5-bromo-4-(2-propynylamino)-2-pyrimidinyl)amino)phenyl)methyl)-2,2,2-trifluoro-acetamide	429 (ESI-MS)
49	*N*-((4-((5-bromo-2-((4-(((2,2,2-trifluoroacetyl)-amino)methyl)phenyl)amino)-4-pyrimidinyl)-amino)phenyl)methyl)-2,2,2-trifluoro-acetamide	592 (ESI-MS)
50	5-bromo-*N2*-(4-(dimethylamino)phenyl)-*N4*-2-propynyl-2,4-pyrimidinediamine	347 (ESI-MS)

51	5-bromo-*N2*-(4-(4-bromo-1-methyl-*1H*-pyrazol-3-yl)phenyl)-*N4*-2-propynyl-2,4-pyrimidine-diamine	463 (ESI-MS)
52	5-bromo-*N2*-(3-((dimethylamino)methyl)phenyl)-*N4*-2-propynyl-2,4-pyrimidinediamine	361 (ESI-MS)
53	5-bromo-*N2*-(4-(4,5-dichloro-*1H*-imidazol-1-yl)phenyl)-*N4*-2-propynyl-2,4-pyrimidinediamine	439 (ESI-MS)
54	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(4-(4-pyridinylmethyl)phenyl)-2,4-pyrimidine-diamine	451 (ESI-MS)
55	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(3-(*1H*-pyrazol-3-yl)phenyl)-2,4-pyrimidinediamine	426 (ESI-MS)
56	5-bromo-*N2*-(4-((dimethylamino)methyl)phenyl)-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidine-diamine	417 (ESI-MS)
57	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(4-(4-morpholinylmethyl)phenyl)-2,4-pyrimidine-diamine	459 (ESI-MS)
58	5-bromo-*N2*-(3-((dimethylamino)methyl)phenyl)-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	417 (ESI-MS)
59	5-bromo-*N2*-(4-(4,5-dichloro-*1H*-imidazol-1-yl)phenyl)-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	495 (ESI-MS)
60	5-bromo-*N2*-(4-(1-piperidinyl)phenyl)-*N4*-2-propynyl-2,4-pyrimidinediamine	387 (ESI-MS)
61	5-bromo-*N4*-2-propynyl-*N2*-(4-(4-pyridinyl-methyl)phenyl)-2,4-pyrimidinediamine	395 (ESI-MS)
62	5-bromo-*N4*-2-propynyl-*N2*-(3-(*1H*-pyrazol-3-yl)phenyl)- 2,4-pyrimidinediamine	370 (ESI-MS)
63	5-bromo-*N4*-2-propynyl-*N2*-(4-(1-pyrrolidinyl-methyl)phenyl)-2,4-pyrimidinediamine	387 (ESI-MS)
64	5-bromo-*N2*-(4-((2,5-dihydro-*1H*-pyrrol-1-yl)-methyl)phenyl)-*N4*-2-propynyl-2,4-pyrimidine-diamine	385 (ESI-MS)
65	5-bromo-*N4*-2-propynyl-*N2*-(3-(1-pyrrolidinyl-methyl)phenyl)-2,4-pyrimidinediamine	387 (ESI-MS)
66	5-bromo-*N2*-(3-((2,5-dihydro-*1H*-pyrrol-1-yl)methyl)phenyl)-*N4*-2-propynyl-2,4-pyrimidine-diamine	385 (ESI-MS)
67	5-bromo-*N2*-(3-(4-morpholinylmethyl)phenyl)-*N4*-2-propynyl-2,4-pyrimidinediamine	403 (ESI-MS)
68	5-bromo-*N2*-(3-(4-bromo-1-methyl-*1H*-pyrazol-3-yl)phenyl)-*N4*-2-propynyl-2,4-pyrimidine-diamine	463 (ESI-MS)
69	5-bromo-*N2*-(3-(1-methyl-*1H*-pyrazol-3-yl)-phenyl)-*N4*-2-propynyl-2,4-pyrimidinediamine	384 (ESI-MS)
70	5-bromo-*N2*-(4-((2,5-dihydro-*1H*-pyrrol-1-yl)methyl)phenyl)-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)- 2,4-pyrimidinediamine	441 (ESI-MS)
71	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(3-(1-pyrrolidinylmethyl)phenyl)-2,4-pyrimidine-diamine	443 (ESI-MS)

72	5-bromo-*N2*-(3-((2,5-dihydro-*1H*-pyrrol-1-yl)methyl)phenyl)-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	441 (ESI-MS)
73	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(3-(4-morpholinylmethyl)phenyl)-2,4-pyrimidine-diamine	459 (ESI-MS)
74	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(4-(4-methyl-1-piperazinyl)phenyl)-2,4-pyrimidine-diamine	458 (ESI-MS)
75	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(4-(4-morpholinyl)phenyl)-2,4-pyrimidinediamine	445 (ESI-MS)
76	5-bromo-*N2*-(3-(4-bromo-1-methyl-*1H*-pyrazol-3-yl)phenyl)-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	519 (ESI-MS)
77	5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(3-(1-methyl-*1H*-pyrazol-3-yl)phenyl)-2,4-pyrimidinediamine	440 (ESI-MS)
78	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-azetidine-ethanol	434 (ESI-MS)
79	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-azetidineethanol	434 (ESI-MS)
80	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-methyl-1-piperazineethanol	477 (ESI-MS)
81	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(phenylmethyl)-1-piperidineethanol	552 (ESI-MS)
82	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-(phenylmethyl)-1-piperidineethanol	552 (ESI-MS)
83	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-pyrrolidineethanol	448 (ESI-MS)
84	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(dipropylamino)-2-propanol	478 (ESI-MS)
85	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-methyl-1-piperidineethanol	476 (ESI-MS)
86	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-morpholineethanol	464 (ESI-MS)
87	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(3-pyridinylmethyl)amino)-2-propanol	499 (ESI-MS)
88	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(4-pyridinylmethyl)amino)-2-propanol	499 (ESI-MS)
89	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3,6-dihydro-1*(2H)*-pyridineethanol	460 (ESI-MS)

90	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-ethyl-1-piperazineethanol	491 (ESI-MS)
91	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(di-2-propenylamino)-2-propanol	474 (ESI-MS)
92	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(2-methylpropyl)amino)-2-propanol	464 (ESI-MS)
93	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-2,5-dihydro-*1H*-pyrrole-1-ethanol	446 (ESI-MS)
94	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)propylamino)-2-propanol	494 (ESI-MS)
95	4-(3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)-2-piperazinone	477 (ESI-MS)
96	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(phenylmethyl)amino)-2-propanol	498 (ESI-MS)
97	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propynylamino)-2-propanol	446 (ESI-MS)
98	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propenylamino)-2-propanol	448 (ESI-MS)
99	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-(dimethylamino)ethyl)ethylamino)-2-propanol	493 (ESI-MS)
100	2-((3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)-methylamino)-N,N-dimethyl-acetamide	493 (ESI-MS)
101	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)methylamino)-2-propanol	466 (ESI-MS)
102	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(butylmethylamino)-2-propanol	464 (ESI-MS)
103	((3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-acetonitrile	447 (ESI-MS)
104	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-furanylmethyl)methylamino)-2-propanol	488 (ESI-MS)
105	2-((3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-acetamide	465 (ESI-MS)
106	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methoxyethyl)amino)-2-propanol	480 (ESI-MS)
107	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)

108	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)
109	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1,3-dihydro-*2H*-isoindole-2-ethanol	496 (ESI-MS)
110	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-thiomorpholineethanol	480 (ESI-MS)
111	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((cyclopropylmethyl)propylamino)-2-propanol	490 (ESI-MS)
112	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methyl-2-propenyl)amino)-2-propanol	476 (ESI-MS)
113	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-piperidineethanol	462 (ESI-MS)
114	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-pyrrolidineethanol	448 (ESI-MS)
115	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(dipropylamino)-2-propanol	478 (ESI-MS)
116	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-methyl-1-piperidineethanol	476 (ESI-MS)
117	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-morpholineethanol	464 (ESI-MS)
118	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3,6-dihydro-1(*2H*)-pyridineethanol	460 (ESI-MS)
119	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-ethyl-1-piperazineethanol	491 (ESI-MS)
120	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(di-2-propenylamino)-2-propanol	474 (ESI-MS)
121	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(2-methylpropyl)amino)-2-propanol	464 (ESI-MS)
122	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-2,5-dihydro-*1H*-pyrrole-1-ethanol	446 (ESI-MS)
123	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)propylamino)-2-propanol	494 (ESI-MS)
124	4-(3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)-2-piperazinone	477 (ESI-MS)
125	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-thiazolidineethanol	466 (ESI-MS)

126	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(phenylmethyl)amino)-2-propanol	498 (ESI-MS)
127	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propynylamino)-2-propanol	446 (ESI-MS)
128	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propenylamino)-2-propanol	448 (ESI-MS)
129	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-(dimethylamino)ethyl)ethylamino)-2-propanol	493 (ESI-MS)
130	2-((3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-N,N-dimethyl-acetamide	493 (ESI-MS)
131	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)methylamino)-2-propanol	466 (ESI-MS)
132	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(butylmethylamino)-2-propanol	464 (ESI-MS)
133	((3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-acetonitrile	447 (ESI-MS)
134	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-furanylmethyl)methylamino)-2-propanol	488 (ESI-MS)
135	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methoxyethyl)amino)-2-propanol	480 (ESI-MS)
136	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)
137	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)
138	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1,3-dihydro-*2H*-isoindole-2-ethanol	496 (ESI-MS)
139	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)tetrahydro-1,4-oxazepine-4(*5H*)-ethanol	478 (ESI-MS)
140	α-((3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-thiomorpholineethanol	480 (ESI-MS)
141	((3-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)butylamino)-acetonitrile	489 (ESI-MS)
142	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((cyclopropylmethyl)propylamino)-2-propanol	490 (ESI-MS)
143	1-(3-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methyl-2-propenyl)amino)-2-propanol	476 (ESI-MS)

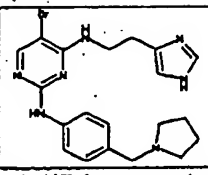
144	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-piperidineethanol	462 (ESI-MS)
145	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-pyrrolidineethanol	448 (ESI-MS)
146	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(dipropylamino)-2-propanol	478 (ESI-MS)
147	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-methyl-1-piperazineethanol	477 (ESI-MS)
148	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-methyl-1-piperidineethanol	476 (ESI-MS)
149	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-morpholineethanol	464 (ESI-MS)
150	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(3-pyridinylmethyl)amino)-2-propanol	499 (ESI-MS)
151	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(4-pyridinylmethyl)amino)-2-propanol	499 (ESI-MS)
152	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3,6-dihydro-1*(2H)*-pyridineethanol	460 (ESI-MS)
153	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-ethyl-1-piperazineethanol	491 (ESI-MS)
154	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(di-2-propenylamino)-2-propanol	474 (ESI-MS)
155	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(2-methylpropyl)amino)-2-propanol	464 (ESI-MS)
156	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-(dimethylamino)ethyl)methylamino)-2-propanol	479 (ESI-MS)
157	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-2,5-dihydro-*1H*-pyrrole-1-ethanol	446 (ESI-MS)
158	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)propylamino)-2-propanol	494 (ESI-MS)
159	4-(3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)-2-piperazinone	477 (ESI-MS)
160	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-thiazolidineethanol	466 (ESI-MS)
161	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(phenylmethyl)amino)-2-propanol	498 (ESI-MS)

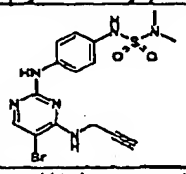
162	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propynylamino)-2-propanol	446 (ESI-MS)
163	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propenylamino)-2-propanol	448 (ESI-MS)
164	2-((3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-N,N-dimethyl-acetamide	493 (ESI-MS)
165	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)methylamino)-2-propanol	466 (ESI-MS)
166	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(butylmethylamino)-2-propanol	464 (ESI-MS)
167	((3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-acetonitrile	447 (ESI-MS)
168	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-furanylmethyl)methylamino)-2-propanol	488 (ESI-MS)
169	2-((3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-acetamide	465 (ESI-MS)
170	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methoxyethyl)amino)-2-propanol	480 (ESI-MS)
171	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)
172	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)
173	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1,3-dihydro-*2H*-isoindole-2-ethanol	496 (ESI-MS)
174	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)tetrahydro-1,4-oxazepine-4(*5H*)-ethanol	478 (ESI-MS)
175	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-thiomorpholineethanol	480 (ESI-MS)
176	((3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)butylamino)-acetonitrile	489 (ESI-MS)
177	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((cyclopropylmethyl)propylamino)-2-propanol	490 (ESI-MS)
178	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methyl-2-propenyl)amino)-2-propanol	476 (ESI-MS)
179	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-piperidineethanol	462 (ESI-MS)

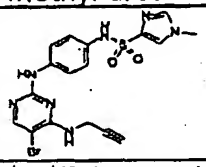
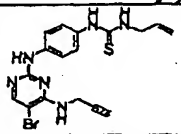
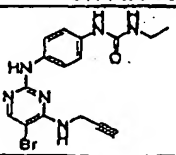
180	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-pyrrolidineethanol	448 (ESI-MS)
181	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(dipropylamino)-2-propanol	478 (ESI-MS)
182	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-methyl-1-piperazineethanol	477 (ESI-MS)
183	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-methyl-1-piperidineethanol	476 (ESI-MS)
184	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-morpholineethanol	464 (ESI-MS)
185	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(3-pyridinylmethyl)amino)-2-propanol	499 (ESI-MS)
186	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(4-pyridinylmethyl)amino)-2-propanol	499 (ESI-MS)
187	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3,6-dihydro-1*(2H)*-pyridineethanol	460 (ESI-MS)
188	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-ethyl-1-piperazineethanol	491 (ESI-MS)
189	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(di-2-propenylamino)-2-propanol	474 (ESI-MS)
190	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(2-methylpropyl)amino)-2-propanol	464 (ESI-MS)
191	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-2,5-dihydro-*1H*-pyrrole-1-ethanol	446 (ESI-MS)
192	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1-azetidineethanol	434 (ESI-MS)
193	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)propylamino)-2-propanol	494 (ESI-MS)
194	4-(3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)-2-piperazinone	477 (ESI-MS)
195	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-thiazolidineethanol	466 (ESI-MS)
196	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl(phenylmethyl)amino)-2-propanol	498 (ESI-MS)
197	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propynylamino)-2-propanol	446 (ESI-MS)

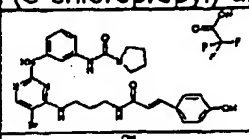
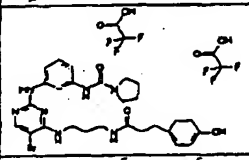
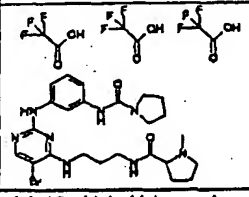
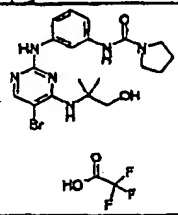
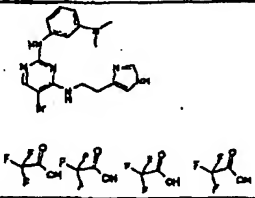
198	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(methyl-2-propenylamino)-2-propanol	448 (ESI-MS)
199	2-((3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-N,N-dimethyl-acetamide	493 (ESI-MS)
200	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-methoxyethyl)methylamino)-2-propanol	466 (ESI-MS)
201	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(butylmethylamino)-2-propanol	464 (ESI-MS)
202	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((2-furanylmethyl)methylamino)-2-propanol	488 (ESI-MS)
203	2-((3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)methylamino)-acetamide	465 (ESI-MS)
204	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methoxyethyl)amino)-2-propanol	480 (ESI-MS)
205	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)
206	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-3-(dimethylamino)-1-pyrrolidineethanol	491 (ESI-MS)
207	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-1,3-dihydro-2*H*-isoindole-2-ethanol	496 (ESI-MS)
208	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)tetrahydro-1,4-oxazepine-4(5*H*)-ethanol	478 (ESI-MS)
209	α-((4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)methyl)-4-thiomorpholineethanol	480 (ESI-MS)
210	((3-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-2-hydroxypropyl)butylamino)-acetonitrile	489 (ESI-MS)
211	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-((cyclopropylmethyl)propylamino)-2-propanol	490 (ESI-MS)
212	1-(4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)amino)phenoxy)-3-(ethyl(2-methyl-2-propenyl)amino)-2-propanol	476 (ESI-MS)
213	*N*-(4-((5-bromo-4-((2-(1*H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-2,2,2-trifluoroacetamide	471 (ESI-MS)
214	*N2*-(4-aminophenyl)-5-bromo-*N4*-(2-(1*H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	375 (ESI-MS)
215	*N2*-(4-aminophenyl)-*N4*-2-propynyl-5-(trifluoromethyl)-2,4-pyrimidinediamine	308 (ESI-MS)

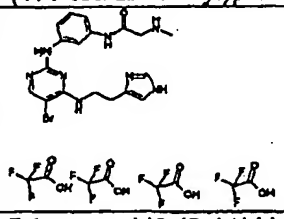
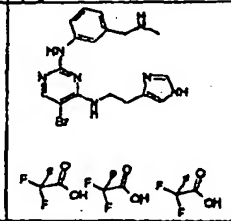
216	*N*-(2-(4-((5-bromo-4-(2-propynylamino)-2-pyrimidinyl)amino)phenyl)ethyl)-2,2,2-trifluoro-acetamide	443 (ESI-MS)
217	2,2,2-trifluoro-*N*-(4-((4-(2-propynylamino)-5-(trifluoromethyl)-2-pyrimidinyl)amino)phenyl)-acetamide	404 (ESI-MS)
218	*N*-((4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-methyl)-2,2,2-trifluoro-acetamide	485 (ESI-MS)
219	*N2*-(4-(aminomethyl)phenyl)-5-bromo-*N4*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	389 (ESI-MS)
220	*N2*-(4-(2-aminoethyl)phenyl)-5-bromo-*N4*-2-propynyl-2,4-pyrimidinediamine	347 (ESI-MS)
221	*N*-(2-(4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-ethyl)-2,2,2-trifluoro-acetamide	499 (ESI-MS)
222	2,2,2-trifluoro-*N*-((4-((4-(2-propynylamino)-5-(trifluoromethyl)-2-pyrimidinyl)amino)phenyl)-methyl)-acetamide	418 (ESI-MS)
223	*N*-methyl-4-((4-(2-propynylamino)-5-(trifluoro-methyl)-2-pyrimidinyl)amino)-benzenemethane-sulfonamide	400 (ESI-MS)
224	*N2*-(4-(aminomethyl)phenyl)-*N4*-2-propynyl-5-(trifluoromethyl)-2,4-pyrimidinediamine	322 (ESI-MS)
225	2,2,2-trifluoro-*N*-(2-(4-((4-(2-propynylamino)-5-(trifluoromethyl)-2-pyrimidinyl)amino)phenyl)-ethyl)-acetamide	432 (ESI-MS)
226	4-((5-bromo-4-(2-propynyloxy)-2-pyrimidinyl)-amino)-benzeneacetic acid ethyl ester	391 (ESI-MS)
227	4-((5-bromo-4-ethoxy-2-pyrimidinyl)amino)-benzeneacetic acid ethyl ester	381 (ESI-MS)

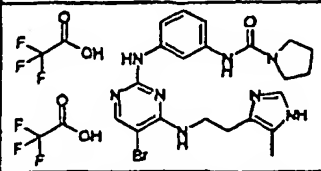
228		443 (ESI-MS)	
229	4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzamide	402 (ESI-MS)	
230	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzenemethanol	389 (ESI-MS)	
231	5-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-2-methoxy-phenol	405 (ESI-MS)	
232	4-((4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-5-iodo-2-pyrimidinyl)amino)-benzenesulfonamide	485 (ESI-MS)	
233	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzamide	402 (ESI-MS)	
234	*N*-(4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-4-morpholinecarboxamide	487 (ESI-MS)	
235	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzenesulfonamide	438 (ESI-MS)	
236	*N2*-(3-(aminomethyl)phenyl)-5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	388 (ESI-MS)	
237	5-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-1,3-dihydro-2H-benzimidazol-2-one	415 (ESI-MS)	
238	*N*-(4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-urea	417 (ESI-MS)	
239	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)- benzoic acid methyl ester	417 (ESI-MS)	

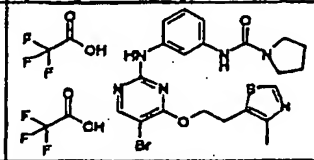
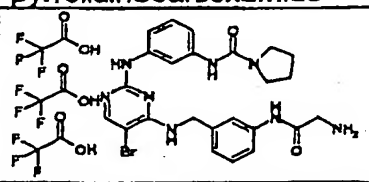
240	3-amino-5-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)- benzoic acid methyl ester	432 (ESI-MS)	
241	*N*-((3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)methyl)-methanesulfonamide	466 (ESI-MS)	
242	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzoic acid	403 (ESI-MS)	
243	4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)- benzoic acid methyl ester	417 (ESI-MS)	
244	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-urea	417 (ESI-MS)	
245	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	471 (ESI-MS)	
246	*N*-((4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)methyl)-urea	431 (ESI-MS)	
247	*N*-((3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)methyl)-urea	432 (ESI-MS)	
248		426 (ESI-MS)	
249	4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzoic acid	403 (ESI-MS)	
250	4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzeneacetic acid	417 (ESI-MS)	
251	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzeneacetic acid	417 (ESI-MS)	
252	5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(3-methylphenyl)-2,4-pyrimidinediamine	373 (ESI-MS)	
253	1-((3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)methyl)-2-pyrrolidinemethanol	471 (ESI-MS)	
254	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-phenol	374 (ESI-MS)	

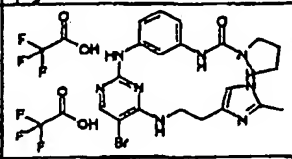
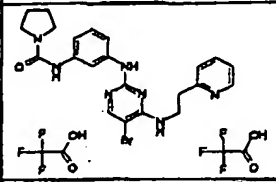
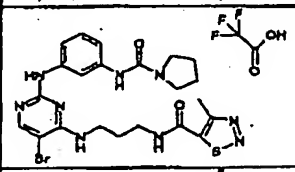
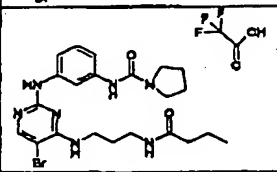
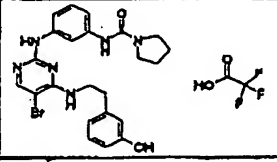
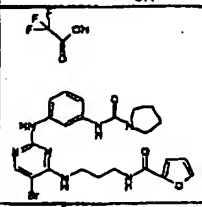
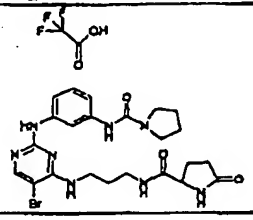
255	1-((3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)methyl)-3-pyrrolidinol	458 (ESI-MS)	
256	5-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-*1H*-isoindole-1,3(2H)-dione	428 (ESI-MS)	
257	*N'*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-N,*N*-dimethyl-urea	445 (ESI-MS)	
258	(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-carbamic acid methyl ester	432 (ESI-MS)	
259	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-methyl-urea	431 (ESI-MS)	
260		463 (ESI-MS)	
261	(4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-carbamic acid methyl ester	432 (ESI-MS)	
262	*N2*-1,3-benzodioxol-5-yl-5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	403 (ESI-MS)	
263		418 (ESI-MS)	
264	*N2*-(3-aminophenyl)-5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	373 (ESI-MS)	
265	3-amino-5-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzoic acid	418 (ESI-MS)	
266	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-cyclopropyl-urea	458 (ESI-MS)	
267	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-4-morpholinecarboxamide	488 (ESI-MS)	
268	*N'*-(3-((4-((3-aminopropyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-N,*N*-dimethyl-urea	409 (ESI-MS)	
269	4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-benzeneacetamide	417 (ESI-MS)	
270		390 (ESI-MS)	

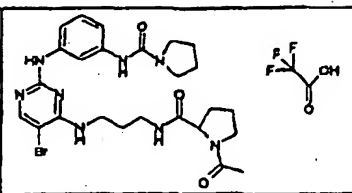
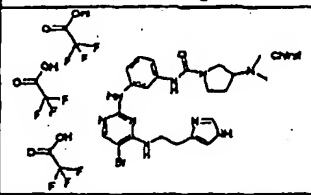
271	(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-carbamic acid 1-methylethyl ester	459 (ESI-MS)	
272	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-(3-chloropropyl)-urea	459 (ESI-MS)	
273			
274			
275			
276	*N*-(3-((4-((4-aminobutyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	448 (ESI-MS)	
277			
278	5-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-2-hydroxy-benzoic acid	419 (ESI-MS)	
279	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-methanesulfonamide	452 (ESI-MS)	
280	3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-phenol	375 (ESI-MS)	
281	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-piperidinecarboxamide	485 (ESI-MS)	
282			
283	*N*-(4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)benzoyl)-glycine	460 (ESI-MS)	

284	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-5-(trifluoromethyl)phenyl)-ethanimidamide	482 (ESI-MS)	
285	*N2*-(3-amino-5-(trifluoromethyl)phenyl)-5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	441 (ESI-MS)	
286	4-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)-amino)-2-pyrimidinyl)amino)-N,*N*-dimethyl-benzeneacetamide	443 (ESI-MS)	
287	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-(2-(4-morpholinyl)ethyl)-urea	529 (ESI-MS)	
288	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-3-hydroxy-1-pyrrolidinecarboxamide	487 (ESI-MS)	
289	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-2-(hydroxymethyl)-1-pyrrolidinecarboxamide	501 (ESI-MS)	
290	*N*-(5-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-2-methylphenyl)-1-pyrrolidinecarboxamide	485 (ESI-MS)	
291	*N*-(3-((4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-5-methyl-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	406 (ESI-MS)	
292	5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(4-(*1H*-tetrazol-5-yl)phenyl)-2,4-pyrimidinediamine	427 (ESI-MS)	
293			
294	5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-*N2*-(4-(2-oxo-2-(1-piperidinyl)ethyl)phenyl)-2,4-pyrimidinediamine	483 (ESI-MS)	
295	*N*-(3-((4-((4-aminobutyl)amino)-5-methyl-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	383 (ESI-MS)	
296			
297	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-phenyl-urea	493 (ESI-MS)	

298	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-3-hydroxy-1-pyrrolidinecarboxamide	487 (ESI-MS)	
299	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-2-(hydroxymethyl)-1-pyrrolidinecarboxamide	501 (ESI-MS)	
300	*N2*-(3-amino-5-chlorophenyl)-5-bromo-*N2*-(2-(*1H*-imidazol-4-yl)ethyl)-2,4-pyrimidinediamine	407 (ESI-MS)	
301	(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-carbamic acid 2-(4-morpholinyl)ethyl ester	530 (ESI-MS)	
302			
303	*N*-(3-((5-bromo-4-((3-(((phenylamino)carbonyl)amino)propyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	552 (ESI-MS)	
304	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-2-methyl-1-pyrrolidinecarboxamide	485 (ESI-MS)	
305	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)-4-fluorophenyl)-1-pyrrolidinecarboxamide	489 (ESI-MS)	
306	*N*-(3-((4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	392 (ESI-MS)	
307	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-2,5-dihydro-*1H*-pyrrole-1-carboxamide	469 (ESI-MS)	
308	*N*-(3-((5-ethyl-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	421 (ESI-MS)	
309	*N*-(3-((4-((3-aminopropyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	433 (ESI-MS)	
310	*N*-(3-((5-bromo-4-((4-hydroxybutyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	449 (ESI-MS)	
311	*N*-(3-((5-bromo-4-(((3,4-dihydroxyphenyl)-methyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	499 (ESI-MS)	
312	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-(3-(1-piperidinyl)propyl)-urea	541 (ESI-MS)	

313	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-(2-(1-piperidinyl)ethyl)-urea	527 (ESI-MS)	
314	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-(3-(4-morpholinyl)propyl)-urea	544 (ESI-MS)	
315	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-*N'*-(4-hydroxycyclohexyl)-urea	514 (ESI-MS)	
316			
317	*N*-(3-((5-chloro-4-((3-((methylsulfonyl)-amino)propyl)amino)-2-pyrimidinyl)-amino)phenyl)-1-pyrrolidinecarboxamide	467 (ESI-MS)	
318	*N*-(3-((5-bromo-4-(((3-nitrophenyl)-methyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	512 (ESI-MS)	
319	*N*-(3-((4-(((3-aminophenyl)methyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	482 (ESI-MS)	
320	*N*-(3-((4-(4-(aminomethyl)-1-piperidinyl)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	395 (ESI-MS)	
321	*N*-(3-((4-((2-(*1H*-benzimidazol-2-yl)ethyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	521 (ESI-MS)	
322			
323	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-acetamide	415 (ESI-MS)	
324	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-benzamide	477 (ESI-MS)	
325	*N*-(3-((5-bromo-4-((2-(*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-propanamide	429 (ESI-MS)	
326	*N*-(3-((5-bromo-4-((3-pyridinylmethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	467 (ESI-MS)	
327	*N*-(3-((5-bromo-4-((4-hydroxycyclohexyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	474 (ESI-MS)	

328	*N*-(3-((5-bromo-4-((2-(1-methyl-*1H*-imidazol-4-yl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	485 (ESI-MS)	
329	*N*-(3-((5-bromo-4-((2-hydroxy-1-(*1H*-imidazol-4-ylmethyl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	501 (ESI-MS)	
330			
331			
332			
333			
334			
335			
336			

337			
338			
339	*N*-(3-((5-bromo-4-((3-((2-thienylcarbonyl)-amino)propyl)amino)-2-pyrimidinyl)amino)-phenyl)-1-pyrrolidinecarboxamide	544 (ESI-MS)	
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342	*N*-(3-((5-bromo-2-((3-((1-pyrrolidinylcarbonyl)-amino)phenyl)amino)-4-pyrimidinyl)amino)-propyl)-3-pyridinecarboxamide	538 (ESI-MS)	
343	*N*-(3-((5-bromo-2-((3-((1-pyrrolidinylcarbonyl)-amino)phenyl)amino)-4-pyrimidinyl)amino)-propyl)-2-pyridinecarboxamide	538 (ESI-MS)	
344	*N*-(3-((5-bromo-2-((3-((1-pyrrolidinylcarbonyl)-amino)phenyl)amino)-4-pyrimidinyl)amino)-propyl)-2-pyrazinecarboxamide	539 (ESI-MS)	
345	*N*-(3-((5-bromo-2-((3-((1-pyrrolidinylcarbonyl)-amino)phenyl)amino)-4-pyrimidinyl)amino)-propyl)-5-pyrimidinecarboxamide	539 (ESI-MS)	
346	(2-((3-((5-bromo-2-((3-((1-pyrrolidinylcarbonyl)-amino)phenyl)amino)-4-pyrimidinyl)amino)-propyl)amino)-2-oxoethyl)methyl-carbamic acid 1,1-dimethylethyl ester	604 (ESI-MS)	
347	(2-((3-((5-bromo-2-((3-((1-pyrrolidinylcarbonyl)-amino)phenyl)amino)-4-pyrimidinyl)amino)-propyl)amino)-1-(*1H*-indol-3-ylmethyl)-2-oxoethyl)-carbamic acid 1,1-dimethylethyl ester	719 (ESI-MS)	
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349	*N*-(3-((4-((3-(benzoylamino)propyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	537 (ESI-MS)	
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354	*N*-(3-((4-((3-((2-thienylcarbonyl)amino)-propyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	465 (ESI-MS)	
355	*N*-(3-((5-bromo-4-((3-(((3-methyl-2-thienyl)carbonyl)amino)propyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	557 (ESI-MS)	
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357	*N*-(3-((5-bromo-4-((3-((2-thienylcarbonyl)-amino)propyl)amino)-2-pyrimidinyl)amino)-phenyl)-3-hydroxy-1-pyrrolidinecarboxamide	560 (ESI-MS)	
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362	*N*-(3-((4-((3-((2-amino-3-(4-hydroxyphenyl)-1-oxopropyl)amino)propyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidine-carboxamide	596 (ESI-MS)	
363	*N*-(3-((4-((3-((2-amino-1-oxo-3-phenylpropyl)-amino)propyl)amino)-5-bromo-2-pyrimidinyl)-amino)phenyl)-1-pyrrolidinecarboxamide	580 (ESI-MS)	
364	*N*-(3-((5-bromo-2-((3-((1-pyrrolidinylcarbonyl)-amino)phenyl)amino)-4-pyrimidinyl)amino)-propyl)-1,2,3,4-tetrahydro-3-isoquinoline-carboxamide	592 (ESI-MS)	
365	*N*-(3-((4-((3-((2-amino-2-phenylacetyl)amino)-propyl)amino)-5-bromo-2-pyrimidinyl)amino)-phenyl)-1-pyrrolidinecarboxamide	566 (ESI-MS)	

366	*N*-(3-((4-((3-(acetylamino)propyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	475 (ESI-MS)	
367	*N*-(3-((5-bromo-4-((3-((2-methoxyacetyl)-amino)propyl)amino)-2-pyrimidinyl)amino)-phenyl)-1-pyrrolidinecarboxamide	505 (ESI-MS)	
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369	*N*-(3-((5-bromo-4-((3-((1-oxopropyl)amino)-propyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	489 (ESI-MS)	
370	*N*-(3-((5-bromo-4-((3-((2-phenylacetyl)-amino)propyl)amino)-2-pyrimidinyl)-amino)phenyl)-1-pyrrolidinecarboxamide	551 (ESI-MS)	
371	*N*-(3-((4-((3-((2-amino-1-oxo-3-(3-thienyl)-propyl)amino)propyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidine-carboxamide	586 (ESI-MS)	
372	*N*-(3-((5-iodo-4-((3-((2-thienylcarbonyl)-amino)propyl)amino)-2-pyrimidinyl)-amino)phenyl)-1-pyrrolidinecarboxamide	591 (ESI-MS)	
373	3-((3-((5-bromo-2-((3-((1-pyrrolidinyl-carbonyl)amino)phenyl)amino)-4-pyrimidinyl)-amino)propyl)amino)-3-oxo-propanoic acid	519 (ESI-MS)	
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376	*N*-(3-((5-bromo-4-((2-(3-pyridinyl)ethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidine-carboxamide	482 (ESI-MS)	
377	*N*-(3-((4-((3-aminopropyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidine-carboxamide	433 (ESI-MS)	
378	*N*-(3-((5-bromo-4-((2-hydroxyethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidine-carboxamide	420 (ESI-MS)	
379	*N*-(3-((4-((3-(aminomethyl)phenyl)amino)-5-bromo-2-pyrimidinyl)amino)phenyl)-1-pyrrolidinecarboxamide	482 (ESI-MS)	
380	*N*-(3-((5-bromo-4-((4-piperidinylmethyl)amino)-2-pyrimidinyl)amino)phenyl)-1-pyrrolidine-carboxamide	474 (ESI-MS)	
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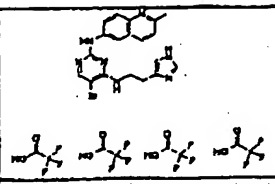
382			
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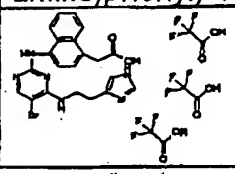
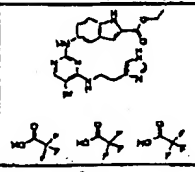
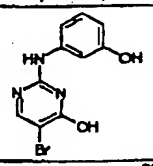
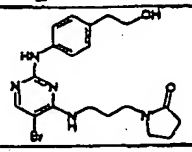
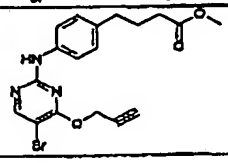
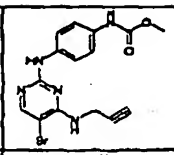
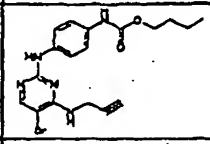
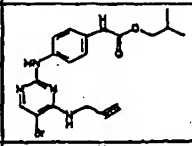
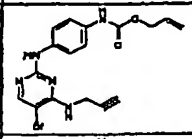
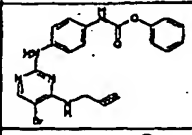
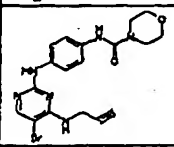
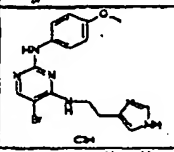
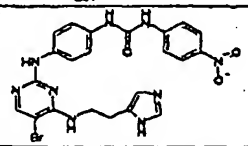
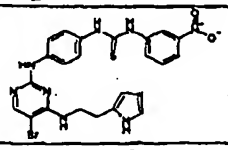
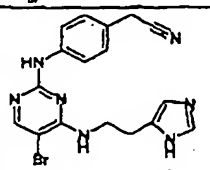
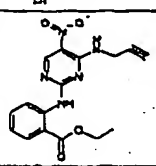
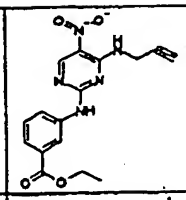
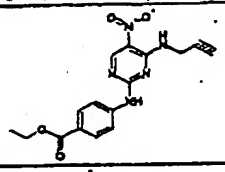
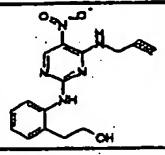
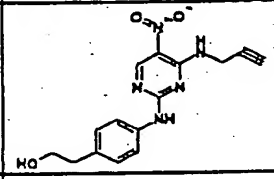
387	*N*-(3-((5-bromo-4-((3-(((5-nitro-2-thienyl)-carbonyl)amino)propyl)amino)-2-pyrimidinyl)-amino)phenyl)-1-pyrrolidinecarboxamide	588 (ESI-MS)	
388	*N*-(3-((5-bromo-4-((3-(((5-bromo-2-thienyl)-carbonyl)amino)propyl)amino)-2-pyrimidinyl)-amino)phenyl)-1-pyrrolidinecarboxamide	621 (ESI-MS)	
389			
390			
391		283 (ESI-MS)	
392		435 (ESI-MS)	
393		405 (ESI-MS)	

394		377 (ESI-MS)	
395		419 (ESI-MS)	
396		419 (ESI-MS)	
397		403 (ESI-MS)	
398		439 (ESI-MS)	
399		433 (ESI-MS)	
400		(ESI-MS)	
401		539 (ESI-MS)	
402		555 (ESI-MS)	
403		399 (ESI-MS)	
404		342 (ESI-MS)	

405		342 (ESI-MS)	
406		342 (ESI-MS)	
407		314 (ESI-MS)	
408		314 (ESI-MS)	

B. Inhibition of Pdk/Akt activity

B 1 General remarks

Compounds described herein, potently block an assay in which phosphoinositide-dependent kinase-1 (PDK-1) mediates the activation of AKT, whose activity is measured in the assay. The compounds, therefore, can be blocking the assay by inhibiting PDK-1 enzyme activity, AKT enzyme activity, or the activation of AKT by PDK-1. These compounds are expected to be therapeutically useful in cancer by inhibiting processes critical for tumor progression, including cell proliferation, survival, and tumor angiogenesis (Testa and Bellacosa 2001; Vivanco and Sawyers 2002). As described herein, compounds blocking block colony formation and/or growth of PC-3 prostate and MDA-468 breast cancer cells in soft agar, which is an in vitro measure of potential anti-tumor activity. Furthermore, the compounds described herein are expected to sensitize tumors to the effects of other chemotherapeutic agents and radiation (Page, Lin et al. 2000; Brognard, Clark et al. 2001).

PDK-1 is a Ser/Thr kinase that functions to phosphorylate and activate other Ser/Thr kinases in the AGC kinase family (Vanhaesebroeck and Alessi 2000). The best-characterized substrate of PDK-1 is the intracellular Serine/Threonine kinase AKT, whose expression and/or activity is elevated in many cancers. Kinase activity of serum and glucocordicoid regulated kinase (SGK), which is structurally related to AKT, can also be phosphorylated and activated by PDK-1. Once activated in tumors, AKT promotes increase tumor cell survival, drug resistance, growth and angiogenesis. Three highly related isoforms of AKT, termed AKT1, AKT2 and AKT3 are known in humans. Activation of AKT is dependent on the activity of phosphatidylinsoitol-3 kinase (PI-3 kinase), whose activity is activated by many signaling molecules elevated in cancer cells, including growth factor receptors (e.g., epidermal growth factor (EGF) receptor,

ErbB2 and IGF1-receptor) and oncogenes (e.g, Ras, BCR-abl, and Src). Other potential substrates of PDK-1 include p70 S6 kinase, p90 S6 kinase, protein kinase C, cAMP-dependent protein kinase (PKA), PRK1, Protein kinase G and serum and glucocorticoid regulated kinase (SGK).

PDK-1-mediated phosphorylation of AKT, which is largely in an inactive form in unstimulated cells, converts the enzyme to a catalytically active form. This occurs through the phosphorylation of the activation loop domain of AKT e.g., at Threonine-309 in AKT2 and Theonine-308 in AKT1. Phosphorylation of a homologous domain in many kinases is known to regulate their kinase activity. One stimulus for PDK-1 mediated phosphorylation of AKT is the association PI-3 kinase products (3,4,5)PIP_3 or (3,4)PIP_2 with the pleckstrin homology (PH) domain of AKT. Although AKT displays low, basal levels of activation in normal, unstimulated cells, AKT often becomes constitutively activated in tumor cells. This occurs through the up-regulation of a variety of different signaling molecules or the presence of oncogenenic mutations commonly found in cancer cells that can promote the activation of AKT, such as PI-3 kinase, growth factor receptors (e.g., EGFR family members), Ras, Src, and BCR-ABL activation. Loss of the tumor suppressor PTEN is another means of greatly increasing AKT activity in cancer cells (Besson, Robbins et al. 1999). PTEN mutation or down regulation of PTEN protein is found in a large number of tumors and cancer cell lines. PTEN is a phosphatase that removes the D-3 phosphate from the products of PI-3 kinase such as phosphatidylinositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate (Myers, Pass et al. 1998; Stambolic, Suzuki et al. 1998). Loss of PTEN, therefore, has the effect of increasing products of PI-3 kinase and promoting constitutive activation of AKT. Cancers with highly up-regulated levels of AKT may be especially sensitive to the effects of PDK-1/AKT pathway inhibitors.

Downstream substrates of PDK-1 and/or AKT are associated with a number of cell responses including proliferation, metabolism and cell survival (Testa and Bellacosa 2001; Vivanco and Sawyers 2002). Examples of signaling molecules downstream from PDK-1 or AKT involved in these pathways include BAD, p70 S6 kinase, p21(Waf-1/Cip-1), Forkhead transcription factors, p27(kip-1), GSK-3-alpha/beta, TSC2 (tuberin), and ecNOS. The survival function of AKT is particularly well-characterized cellular activity of AKT (Datta, Brunet et al. 1999). AKT functions to suppress apoptosis induced by a variety of agents, including UV radiation, chemotherateutic drugs, TFG-beta, withdrawal of survival factors, overexpression of oncogenes such as c-myc and detachment of cells from the extracellular matrix.

The ability to escape cell death, also termed apoptosis, is critical characteristic of tumor cells allowing their uncontrolled growth and invasive behavior. One trigger for apoptosis is the perturbation of the normal growth regulation resulting from oncogenic mutations or inappropriate expression signaling molecules coupled to cell proliferation. Apoptotic pathways, therefore, provide a key means of protection from the development and progression of cancer. Cancer cells, however, can escape apoptotic death by selecting for activation of signaling molecules such as AKT that turn off apoptotic signals. Some oncogenes, such as Ras, which is activated in as many as 60% of human tumors, simultaneously promote uncontrolled growth and the activation of AKT. Inhibition of AKT in HIH 3T3 cells prevents transformation of these cells through transfection with activated Ras. Furthermore, a number of studies have shown that combining expression an oncogene with an activated form of AKT greatly facilitates formation of tumors in vivo (e.g., (Holland, Celestino et al. 2000)). Inhibitors of PDK-1, by blocking activation of AKT, are a means of promoting apoptosis in tumors cells, especially, but not necessarily limited to those over-expressing AKT activity. By blocking cell survival mechanisms, the compounds described herein could also be

useful to promote sensitivity of cancer cells to radiation therapy and to treatment with a variety of chemotherapeutic agents.

Inhibitors of the PDK-1/AKT pathway are also expected to block cancer progression through inhibition of tumor-stimulated angiogenesis (Dimmeler and Zeiher 2000; Shiojima and Walsh 2002). AKT has been shown to regulate a number of responses critical for the process of angiogeneisis, including endothelial cell migration, proliferation and survival during new vessel formation, ecNOS regulation, response of endothelial cells to growth factors (including IGF-1, agniopoetin-1 and VEGF) and the regulation of hypoxia-inducible factor-1 (HIF-1)-alpha levels.

Inhibition of the cell cycle and growth of tumor cells is yet another expected effect of compounds that block PDK-1 and/or AKT. Inhibition of PDK-1 and/or AKT activity has been shown to regulate growth of cancer cells in a number of studies. These effects may occur through PDK-1 or AKT-mediated regulation of a number of different signaling pathways important in growth regulation. For example, AKT has been shown to block nuclear localization and/or expression of the cyclin-dependent kinase inhibitors, p21(Waf-1/Cip-1) and p27(kip-1). Compounds blocking these effects would be expected to reduce the activity of cyclin-dependent kinases, blocking progression through the cell cycle and reducing tumor cell growth. AKT was found to inhibit Myt1, thereby acting as an initiator of mitosis in oocytes fronm the starfish Asterina pectinfera. Furthermore, PDK-1 and/or AKT regulate the expression of proteins important for cell growth through its regulation of mTOR, p70 S6 kinase and eukaryotic initiation factor 4E binding protein 1 (4E-BP1). While the mechanism of this regulation is not firmly established, it has been shown that AKT phosphorylations and reduces expression of TSC2, thereby relieving TSC-2 mediated suppression of mTOR activity. This, in turn, promotes the activation p70 S6 kinase activity and the phosphorylation and inhibition of 4E-BP1 (Inoki, Li et al. 2002; Potter, Pedraza et al. 2002). Both these

effects result in increased synthesis of mRNAs encoding proteins important for cell growth. Loss of TSC2 function is associated with the disease tuberous sclerosis, which results in differentiated benign growths (harmatomas) in a wide variety of organs. PDK-1 also has been shown to have a direct role in the phosphorylation and activation p70 S6 kinase (Alessi, Kozlowski et al. 1998).

In summary, the compounds described which block PDK-1 mediated activation of AKT or PDK-1 directly may be useful therapeutic agents in cancer by blocking a number of processes required for tumor progression, including growth, tumor cell survival, and recruitment of new blood vessels. The compounds described may also enhance the anti-tumor effects of radiation or other chemotherepeutic drugs. The compounds may also be useful for the treatment of tuberous sclerosis. Furthermore, the compounds described could be useful modulators of the immune response (Cantrell 2002) and for the treatment of autoimmune diseases such as rheumatoid arthritis and MS.

B 2 Experimental Procedures

B. 2.1. Cell-based assays

Materials: Prostate cancer cells (PC-3) and breast cancer cells (MDA-468) were obtained from the ATCC (Manassas, VA). Mammalian protein extraction reagent (MPER), Halt protease inhibitor cocktail, BCA protein reagent, and Supersignal Western Chemiluminescent reagent were obtained from Pierce Chemical Co. (Rockford, IL). 10% Tris-Glycine gels (1.0mm, 15-well) and nitrocellulose (0.2 micron) were obtained from Invitrogen Life Technologies (Carlsbad, CA). Agar agar was purchased from EM Science. Polyclonal antibodies raised against phospho-AKT (Thr308, #9275), phospho-AKT (Ser473, #9271), phospho-S6-kinase (Thr389, #9205), and anti-rabbit IgG-HRP conjugate were obtained from Cell Signaling

Technologies (Beverly, MA). Nitroblue tetrazolium reagent and staurosporine were purchased from Sigma Chemical Co. (St. Louis, MO). LY294002 was purchased from Cayman Chemicals (Ann Arbor, MI). All other materials were of reagent-grade quality.

Cell growth conditions: PC-3 cells were grown in F12K medium, supplemented with 7% (v/v) fetal calf serum (fcs) and 2mM glutamine. MDA-468 cells were grown in MEM-alpha, supplemented with 10% (v/v) fcs, 2mM glutamine, 1mM sodium pyruvate, 0.1mM non-essential amino acids, 10mM Hepes, and 1μg/ml insulin. All cell lines were incubated in a 37°C humidified incubator, with a 5% CO_2 atmosphere.

Cell-based assays using Western blot analysis: PC-3 cells were seeded into 24-well plates (Corning Costar) at 100-120,000 cells per well and allowed to grow overnight to 90% confluence. On the next day, the cells were washed once with 1.5ml PBS, and the medium replaced with low serum (0.1% fcs) containing growth medium (starvation medium). After a second overnight incubation, the medium was replaced with 0.5ml/well of starvation medium. Some assays were also conducted in normal growth medium (7% fcs, PC-3, or 10% fcs, MDA-468). Cells were treated with vehicle control (DMSO) or drug at a final DMSO concentration of 1% v/v (a 5μl addition per 0.5ml medium), and cells were allowed to incubate for the stated times. The incubations were terminated by aspiration of the medium, washing the wells with 1.0ml PBS, and lysis in 0.1ml MPER reagent, supplemented with protease inhibitors (Halt reagent) and phosphatase inhibitors (1mM NaF, 1mM sodium vanadate). Cell lysates were briefly centrifuged to remove insoluble debris, and aliquots were taken for protein (BCA) and Western blot analysis. For Western analysis, lysates were combined with Laemmli SDS sample buffer, boiled, and loaded onto 10% Tris-Glylcine gels, normalizing for the amount of protein loaded in each lane. Electrophoresed gels were transferred onto nitrocellulose paper, blocked with 5% milk in Tris-buffered saline

containing 0.1% Tween-20, and incubated overnight with the primary antibody (phospho-AKT-Thr308 @ 1:667, phospho-AKT-Ser473 @ 1:1000, phospho-S6 kinase @ 1:1000). Blots were washed three times with blocking buffer and incubated one hour with anti-rabbit IgG-HRP @ 1:2000. Washed blots were developed using the Supersignal Western Chemiluminescent detection system. Films were scanned using a Bio Rad CCD camera, and phospho-protein bands were quantitated using Bio Rad Quantity-One software.

Soft agar efficacy assays: PC-3 and MDA-468 cells were grown in soft agar over a period of 2 weeks. Culture plates (Corning 35mm x 10mm) were prepared with a bottom layer of 0.5% agar in growth medium, 2ml/well. Cells were trypsinized, dispersed into single cells with a 21-gauge needle, and seeded in a top layer of 0.3% agar/growth medium, 1.5ml/plate, containing 4500 cells per plate. On the following day, the first vehicle or drug treatment was added, in a volume of 1.0ml of 0.3% agar/growth medium, containing 1% DMSO. Drug concentrations were adjusted to reflect the total volume of agar in the plates. The cells were allowed to grow for seven days and treated a second time (adding an additional 1 ml of 0.3% agar). Colonies were visually inspected for growth and viability every few days. On day 12-14, nitroblue tetrazolium (0.5 mg/ml PBS) was added, 0.3 ml per plate, and the viable colonies were allowed to develop color for 1-2 days. Plates were scanned using a Bio Rad CCD camera, and the colonies were quantitated for ony number, and for total stained area, using ImagePro software.

B 2.2. AKT2 and PDK-1 Expression and purification

pHisAKT2 was constructed by cloning AKT2 into pBlueBacHis2A (Invitrogen Corp.) through the BamH1 and Bgl2 restriction sites, forming a fusion protein behind a 38 amino acid N-terminal His tag sequence derived

from the vector. The new N-terminal sequence + first 10 residues of AKT2 is as follows:

MPRGSHHHHHHGMASMTGGQQMGRDLYDDDDKDRWGSMNEVSVIKEG

(AKT2 is underlined and is in bold His-6). Similarly, pHisPDK-1 was constructed by cloning PDK1 into pBlueBacHis2A (Invitrogen Corp.) at EcoR1 cloning site, forming a fusion protein behind an N-terminal His-tag (preceding sequence of ...ICSWYHGILDMARTTSQLYD.... (PDK1 sequence underlined). The new N-terminal sequence + first 10 residues of PDK1 is as follows:

MPRGSHHHHHHGMASMTGGQQMGRDLYDDDDKDRWGSELEICSWYHGIL DMARTTSQLYD... (PDK1 is underlined and His-6 is in bold).

Recombinant baculovirus containing either His-tagged AKT2 or His-tagged PDK-1 cDNAs were prepared by the following method. pHisAKT2 or pHisPDK-1 were cotransfected with Bac-N-Blue (Invitrogen) viral DNA info SF-21 cells and after 3 - 4 days, viral supernatant were isolated and recombinant viruses were plaque purified. His-tagged AKT2 (HisAKT-V) or His-tagged PDK-1 (HisPDK-1-V) cDNA expressing clones were selected and expanded as a stock for use in the expression of recombinant proteins described below.

To express His-tagged AKT2 and PDK-1, a 10 liter suspensions of SF-21 insect cells were infected with recombinant viruses (i.e., either HisPDK-1-V or HisAKT2-V) and cells were harvested 3-4 days post infection and frozen. To purify recombinant His-tagged AKT2 and PDK-1, cell pellets were thawed, homogenized (in phosphate buffered saline (PBS), supplemented with 10% Triton X-100, 0.5 M NaCl, 2 g/l NaF, 2.5 μg/ml aprotinin, 5 μg/ml leupeptin, 1.25 μg/ml pepstatin, 0.1% beta-mecaptoethanol, and 1 mM vanidate, 10 mM imidizole and adjusted to pH 7.6) and were purified using two sequential rounds of Ni2+ affinity chromatography followed by gel filtration. Enzymes were frozen in small aliquots and stored at -80°C in 50 mM Tris-HCl, pH 7.5, 150 mM NaCl, pH

7.5, 0.1 mM EGTA, 0.1 mM EDTA, 0.2 μM benzamidine, 0.1% beta-mercaptoethanol and 0.25 M sucrose.

B 2.3. Enzyme Assays

PDK-1-dependent activation and subsequent enzymatic activity of AKT2: Purified human AKT2 activity was routinely measured in an assay in which the enzyme was first activated by PDK-1 in the presence of phosphatidylinositol-4,5-bisphosphate (PIP2). Once activated, AKT2-dependent phosphorylation of a peptide substrate was measured by scintillation proximity assay (SPA).

Phospholipid vesicles were prepared as follows: 2.2 mg each of phosphatidylcholine (Sigma Cat # P-1287) and phosphatidylserine (Sigma Cat #P-6641) were transferred to a borosilicate glass test tube and dried down under nitrogen. 1 mg of PIP_2 (Biomol Cat #PH-106) was suspended in 9.5 ml of 10 mM HEPES, pH 7.5 and transferred to the dried lipids. The tube was vortexed until a milky suspension was produced. Then the tube was placed in a ice water-jacketed cup horn sonicator (Branson Instruments) and subjected to sonication for 20 min at medium power until a translucent phospholipid vesicle preparation was obtained. Aliquots of the vesicle suspension were frozen at -80°C until needed.

Assays were performed in 96-well polypropylene V-bottom plates. Incubations were carried out for 2 hr at room temperature. The assay mixture contained in a volume of 60μL: 15 mM MOPS, pH 7.2, 1 mg/ml bovine serum albumin, 18 mM betaglycerolphosphate, 0.7 mM dithiothreitol, 3 mM EGTA, 10 mM MgOAc, 7.5 (M ATP, 0.2 μCi of [γ-^{33}P]ATP, 7.5 μM biotinylated peptide substrate (biotin-ARRRDGGGAQPFRPRAATF), 0.5 μL of PIP_2-containing phospholipid vesicles, 60 pg of purified recombinant human PDK-1, and 172 ng of purified recombinant human AKT2. Test compounds were added from

stock solutions in DMSO. The final concentration of DMSO was 2.5%. Following incubation, 10 μL of the assay mixture was transferred to a 96-well clear-bottom polystyrene plate (Wallac Isoplate) containing 0.33 mg of streptavidin-coated SPA beads (Amersham Cat. # RPNQ0007) suspended in 200 μL of phosphate-buffered saline, pH 7.4, containing 50 mM EDTA and 0.1% Triton X-100. After brief shaking, the SPA beads were allowed to settle to the bottom of the plate overnight at room temperature. Product formation, measured in a Wallac MicroBeta scintillation counter, was proportional to the time of incubation and to the amount of PDK-1 and inactive AKT2 added. PDK-1 was added at sub-optimal levels so that the assay could sensitively detect inhibitors of AKT2 activation as well as direct AKT2 kinase inhibitors. The z'-factor for the assay was greater than 0.7.

Phosphorylation of the peptide substrate on the threonine residue was shown to be dependent upon activated AKT2 produced during the incubation. No phosphorylation was observed in the absence of ATP, $Mg^{2}+$, PDK-1, AKT2, or PIP_2-containing vesicles. Phosphorylation was readily observed, however, upon addition of purified activated human AKT1 (purchased from Upstate Biotechnology), independent of the presence or absence of added PDK-1 or PIP_2-containing vesicles.

Direct assay of PDK-1 activity: Recombinant human PDK-1 activity was directly measured using a filter binding protocol. Incubations were performed at room temperature for 4 hr in a final volume of 60 μL containing: 50 mM Tris-HCl, pH 7.5, 0.1 mM EGTA, 0.1 mM EDTA, 0.1% beta-mercaptoethanol, 1 mg/ml bovine serum albumin, 10 mM MgOAc, 10 μM ATP, 0.2 μCi of [γ-^{33}P]ATP, 7.5 μM of substrate peptide (H_2N-ARRRGVTTKTFCGT) and 60 ng of purified human PDK-1. The enzymatic reaction was stopped by addition of 25 mM EDTA. A portion of the reaction mixture was spotted on Whatman P81 phosphocellulose paper. The filter paper was washed 3 times with 0.75% phosphoric acid to

remove unreacted [γ-^{33}P]ATP, and once with acetone. After drying, the filter-bound labeled peptide was quantitated using a Fuji Phosphoimager.

B 3. Results

Compounds, which inhibit Akt/Pdk activity are shown in Fig. 2 and Fig. 3.

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C Inhibition of Chk kinase activity

C.1. General Remarks

The compounds of this invention inhibit the cell cycle checkpoint kinases which are essential for the cellular response to DNA damage and for the coordination of the cell cycle. The DNA damage might be due to external or internal influence. These influences involve - without being limited to them - replication errors, DNA base damages, DNA strand breaks and the exposition to irradiation or cytotoxic chemicals.

The inhibition of one or more of the cell cycle checkpoint kinases is the basis for the effect of the compounds of this invention e.g. against cancer, like solid tumours or leukemia, against other hyperproliferative diseases, e.g. HIV and viral infections, like e.g. cytomegalus-infections, herpes and hepatitis B and C and HIV.

The eukaryotic cell division cycle ensures the duplication of the genome and its correct distribution to the daughter cells by running through a coordinated and regulated sequence of events. The cell cycle is divided in four successive phases: the G1 phase represents the time before the DNA replication, during which the cell is growing and susceptible for external stimuli. During the S-phase the cell replicates its DNA, and in the G2 phase the cell prepares for the entry into the mitosis. During the mitosis (M-Phase) the replicated DNA is separated and the cell division is carried out.

Corresponding to the extraordinary relevance of the cell division cycle the passage through the cycle is strictly regulated and controlled. The enzymes needed for the progression through the cycle, the cyclin-dependent kinases, have to be activated at the right moment and have to be switched off as soon as the corresponding phase is finished. Checkpoint systems

arrest the progression through the cell cycle if DNA damage is detected, the DNA replication is not completed or the building of the spindel apparatus is not completed (Hartwell et al., 1989). They do this by influencing the generation, activation or inactivation of the cyclin-dependent kinases.

Checkpoints permit the cell to track the ordered course of the individual phases of the cell cycle. The most important checkpoints are at the transition from the G1 phase into the S phase and at the transition from the G2 phase into the M phase (for a review see Dasika et al. 1999). The G1 checkpoint ensures that the cell does not start the DNA synthesis if it is not sufficiently nourished or if it does not correctly interact with other cells or with the substrate or if the DNA of the cell is not intact. The G2/M checkpoint ensures that the DNA is completely replicated and the mitotic spindle is build up before the cell enters the mitosis. The G1 checkpoint is controlled by the gene product of the tumour suppressor gene p53. p53 becomes activated after the detection of changes in the metabolism or the genomic integrity of the cell and p53 is able to initiate either a stop of the cell cycle program or apoptosis. For this the transcriptional activation of the expression CDK inhibiting protein p21 plays a crucial role.

A fundamental component of the G2/M checkpoint is the activation of the kinases ATM, Chk1 and Chk2 after a DNA damage and finally the phosphorylation and inactivation of the phosphatase Cdc25C. This results in a cell cycle arrest, as the inhibitory phosphorylation of the amino acids threonine-14 and tyrosine-15 of the cyclin dependent kinase 1 (CDK1) is not further removed by Cdc25C.

The loss of the regulation of the cell cycle and the loss of checkpoint control are characteristic features of tumour cells. p53, which is essential for the G1 checkpoint, is the gene most often mutated in human tumours (about 50 %). In tumour cells expressing unmutated p53, it is often

inactivated by an enhanced proteolytic degradation or the genes of other proteins involved in the G1 checkpoint are mutated or deregulated. Examples are the inactivation of the tumour suppressor genes Rb, $p16^{INK}4$ and $p19^{ARF}$ or the overexpression of the oncogenes HDM-2 and cyclin D (Levine, 1997). In consequence nearly all tumour cells do not have a functional G1 checkpoint which enables the to accumulate further mutations and to escape from a DNA damage induced apoptosis. This inactivation of the G1 checkpoint is an important factor for the genomic instability which drives the evolution of human tumours and crucially contributes to the resistance of tumour cells against chemotherapeutics and irradiation. On the other hand the inactivation of the G1 checkpoint enhances the dependence of the tumour cells on the second important barrier against the cell killing effect of DNA damages, the G2/M checkpoint, and makes the tumour cells especially vulnerable to an abrogation of the G2/M checkpoint (Hartwell und Kastan, 1994, O'Connor und Fan, 1996).

The cell cycle checkpoint kinase Chk1 is an important part of the G2/M checkpoint (Sanchez et al., 1997). Inactivation of Chk1 abrogates a DNA damage induced G2/M arrest and thereby leads to a preferred killing of the resulting checkpoint deficient cells (Takai et al., 2000, Koniaras et al., 2001, Liu et al., 2000). The inactivation of Chk1 causes that Cdc25C stays active despite of the DNA damage and is able to activate Cdk1/CycB, the main effector of the entry into the mitosis. However, due to the persistent DNA damage the cell is not able to complete the M phase successfully and undergoes apoptosis instead ("mitotic catastrophe").
The cell cycle checkpoint kinase Chk2 is also activated by DNA damage (Matsuoka et al. 1998, Chaturvedi et al., 1999) and activated Chk2 phosphorylates and thereby inactivates Cdc25C. Cells without active Chk2 have a defect in their checkpoint response to DNA damage (Hirao et al., 2000).

The inactivation of Chk1 and Chk2 abrogates the G2/M arrest which is induced by damaged DNA and sensitises the resulting checkpoint deficient cells to the killing by DNA damaging events. As cancer cells are more sensitive towards the abrogation of the G2/M checkpoint than normal cells there is great interest in compounds, which inhibit Chk1, Chk2 or Chk1 and Chk2, as a result abrogate the G2/M checkpoint and improve the killing of cancer cells by DNA damaging events. Such DNA damaging events can be the direct damage of the DNA by irradiation or chemotherapeutics, e.g. strandbreaks inducing compounds, DNA-alkylating compounds or topoisomerase inhibitors, the exertion of influence on the building of the mitotic spindle apparatus, hypoxic stress due to limited supply of the tumour with blood - e.g. induced by anti-angiogenic drugs - or also endogenous DNA damages resulting from the genomic instability inherent to cancer cells.

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The following examples describe the biologic effect of the compounds of the invention without limiting the invention to these examples.

C 2 Experimental Procedure

C 2.1. Chk1 kinase assay

Recombinant Chk1-His_6-fusion protein, expressed in insect cells (Sf-9) and purified by Ni-NTA affinity chromatography was used as kinase. Alternatively, commercially available GST-Chk1-fusion protein (Upstate Biotechnology, Dundee, Scotland) can be used. As substrate for the kinase reaction the biotinylated peptide biotin-Arg-Ser-Gly-Leu-Tyr-Arg-Ser-Pro-Ser-Met-Pro-Glu-Asn-Leu-Asn-Arg-Pro-Arg-OH was used which can be purchased e.g. from the company Biosyntan GmbH (Berlin-Buch, Germany).

Chk1 (200 ng/measurement point) was incubated for 60 min at 22°C in the presence of different concentrations of test compounds (0 µM and concentrations in the range 0.001 - 30 µM) in 30 µl assay buffer [50 mM Hepes/NaOH pH7.5, 10 mM $MgCl_2$, 1 mM $MnCl_2$, 0.1 mM sodium ortho-vanadate, 1.0 mM dithiothreitol, 0.5 µM adenosine-tri-phosphate (ATP), 1.9 µM substrate peptide (Biotin-Arg-Ser-Gly-Leu-Tyr-Arg-Ser-Pro-Ser-Met-Pro-Glu-Asn-Leu-Asn-Arg-Pro-Arg-OH), 6 nCi/measurement point ^{33}P-gamma ATP, 0.008% NP40, 1.5% (v/v) dimethylsulfoxide]. The reaction was stopped by the addition of 20 µl of a suspension of streptavidine coated PVT-SPA-beads (0.15 mg/measurement point, from Amersham Biotech) in an aqueous EDTA/ATP-solution (20 mM EDTA, 50 µM ATP, 1 % (v/v) Triton X-100 in PBS).

The resulting mixture was incubated further 16 h at 22°C to allow the binding of the biotinylated peptide to the streptavidine coated

PVT-SPA-beads and to allow the sedimentation of the beads. Subsequently the amount of 33P incorporated into the substrate peptide was evaluated by scintillation measurement in a Topcount NXT (Perkin-Elmer).

C 2.2. Chk2 kinase assay

Recombinant Chk2-His_6-fusion protein, expressed in insect cells (Sf-9) and purified by Ni-NTA affinity chromatography was used as kinase. Alternatively, commercially available GST-Chk2-fusion protein (Upstate Biotechnology, Dundee, Scotland) can be used. As substrate for the kinase reaction the biotinylated peptide biotin-Arg-Ser-Gly-Leu-Tyr-Arg-Ser-Pro-Ser-Met-Pro-Glu-Asn-Leu-Asn-Arg-Pro-Arg-OH was used which can be purchased e.g. from the company Biosyntan GmbH (Berlin-Buch, Germany).

Chk2 (400 ng/measurement point) was incubated for 60 min at 22°C in the presence of different concentrations of test compounds (0 µM and concentrations in the range 0.001 - 30 µM) in 30 µl assay buffer [50 mM Hepes/NaOH pH7.5, 10 mM $MgCl_2$, 1 mM $MnCl_2$, 0.1 mM sodium ortho-vanadate, 1.0 mM dithiothreitol, 1.5 µM adenosine-tri-phosphate (ATP), 8 µM substrate peptide (Biotin-Arg-Ser-Gly-Leu-Tyr-Arg-Ser-Pro-Ser-Met-Pro-Glu-Asn-Leu-Asn-Arg-Pro-Arg-OH), 15 nCi/measurement point ^{33}P-gamma ATP, 0.008% NP40, 1.5% (v/v) dimethylsulfoxide]. The reaction was stopped by the addition of 20 µl of a suspension of streptavidine coated PVT-SPA-beads (0.25 mg/measurement point, from Amersham Biotech) in an aqueous EDTA/ATP-solution (20 mM EDTA, 50 µM ATP, 1 % (v/v) Triton X-100 in PBS).

The resulting mixture was incubated further 16 h at 22°C to allow the binding of the biotinylated peptide to the streptavidine coated PVT-SPA-beads and to allow the sedimentation of the beads.

Subsequently the amount of ^{33}P incorporated into the substrate peptide was evaluated by scintillation measurement in a Topcount NXT (Perkin-Elmer).

C 2.3 FACS-Assay

Human HeLa (ATCC CCL-2) cervix adenocarcinoma cells were plate out to a density of 3000 cells / cm² in DMEM medium containing 10% FCS in 6-well plates. After 48 h incubation the medium was exchange for DMEM medium supplemented with 10% FCS and 5 µg/ml bleomycine sulfate. After 18 h incubation the test compounds were added to final concentrations of 0.03 µM, 0.1µM, 0.3 µM, 1µM,3 µM, 10 µM, or 30 µM. After a further incubation of 24 h or 48 h the cells were collected by trypsinisation, permeablelised and fixed in 70 % ethanol . The DNA was stained with propidium iodide and the cellular DNA-content was measured by a Fluorescence Activated Cell Scan (FACS). The portion of cells with a cellular DNA-content corresponding to the G2 and M phases of the cell cycle was evaluated to judge the effect of the test compound on the bleomycine induced G2/M arrest of the cells.

C 2.4. Expression and purification of Chk1 and Chk2

The coding sequences were cloned by RT-PCR and nested PCR from commercially available polyA-RNA. The primers used for this purpose were designed according to the sequence information in Genebank (AF 016582 for Chk1, AF086904 for Chk2). In preparation for the C-terminal His6-fusion in the respective second PCRs 3'-primers were used, which removed the stop codon at the end of the coding sequence of Chk1 and Chk2 by mutation. Additional restriction sites were added to the primers (EcoRI-sites for the 5'-primers and HindIII-sites for the 3'-primers).

The cDNAs were cloned into the vector pT7-Blue T (Novagen). To introduce the His_6-sequence at the C-terminus of Chk1 and Chk2 EcoRI/HindIII fragments from these pT7-Blue plasmids were cloned into the bacterial expression vector pET23a. From these pET23a-Chk1 und pET23a-Chk1 vectors DNA fragments coding for Chk1-His6 or Chk2-His_6 were excised and inserted into the baculovirus-transfer-vector pVL1392. The generated vectors were transfected into Sf-9 cells with AcNPV baculovirus genomic DNA (BaculoGold Transfection Kit, Pharmingen). The viruses produced by this procedure were plaque-purified and amplified for further infections.

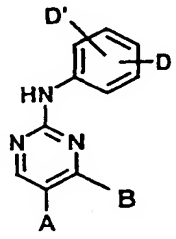
Recombinant Chk1-His_6-fusion protein and recombinant Chk2-His_6-fusion protein were produced in Sf-9-cells. The Sf-9-cells were infected with the viruses at a MOI (Multiplicity of infectivity) = 1 and subsequently cultivated for 3 days in TNM-FH-medium. After lysis of the cells and sedimentation of the cell debris by centrifugation (20000 x g) the fusion proteins were purified from the supernatant by Ni-NTA affinity chromatography (Superflow from QIAGEN, Hilden, Germany) and dialysed into 50 mM Tris/HCl buffer (pH 7.5) containing 150 mM NaCl and 2 mM EDTA. The protein solution was shock frozen and stored at -80°C.

C 3. Results

Compounds, which inhibit Chk activity are shown in Fig. 4-9.

Claims

1. Compounds of general structure (I),



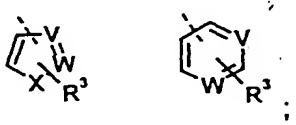
(I)

wherein

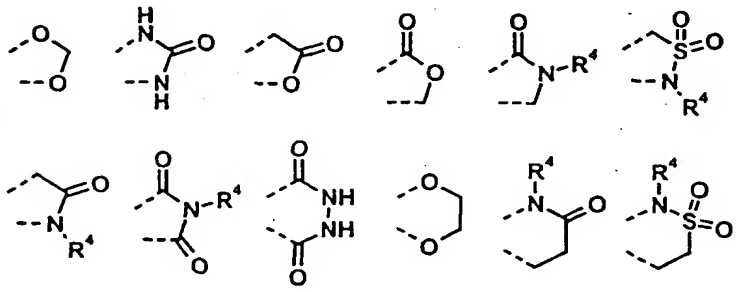
A	Represents	-F, -Cl, -Br, -I, -CN, $-NO_2$, $-CF_3$, CH_3, $-CH_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, or an optionally branched C_3-C_6 alkyl, alkenyl, or alkynyl group, or a C_3-C_6 cycloalkyl group, or an optionally branched C_1-C_3 alkoxy group;
B	Represents	a group **-G-K-Q;**
	or	a group **-G-K-L-M;**
	Or	A group -G-(C_2-C_6 alkylidene)-**M**
	or	a group -G-(C_2-C_6 alkylidene)-**G-L-M;**
D	Represents	up to two substituents indepedently chosen from
		H
		Or **-R^3;**
		Or **-K-U;**
		or **-K-L-U;**
		or **-K-G-K-T-U;**

with the proviso, that between two of the above mentioned substituents, when attached to adjactent carbon atoms, a single bond can be formed, resulting together with the two carbons of the adjactend phenyl ring in a five membered heteroaromatic ring with up to three heteroatoms selected from O, S, N or a six membered heteroaromatic ring with one to three nitrogen atoms, whereby the resulting bicyclic ringsystem is optionally substituted with R^3;

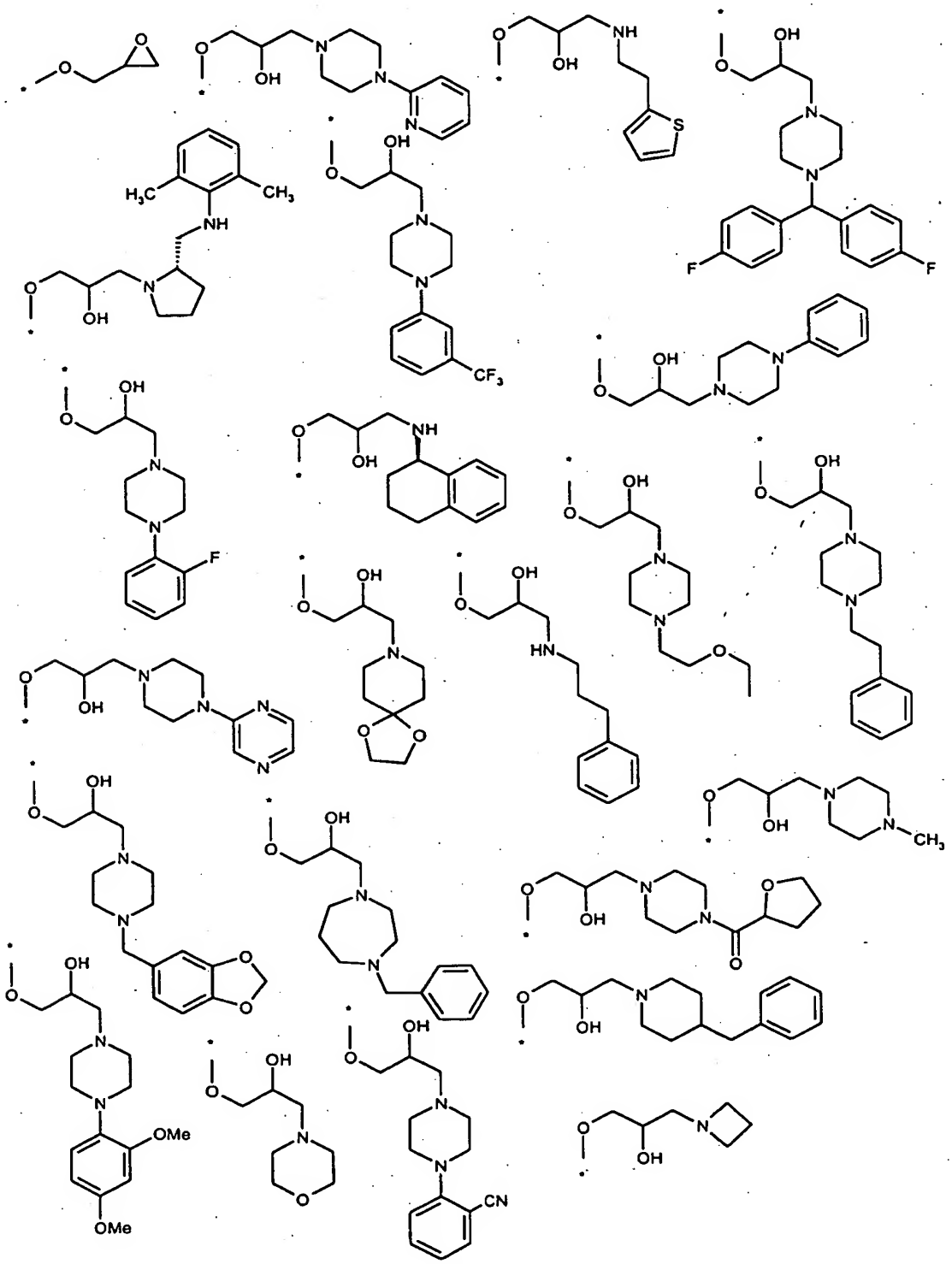
or The groups



Or Two residues **D** combined represent



D' Represents **-K-G-K-T-U,**
except this group stands for the following residues:



Or (C_1-C_6 alkylidene)-**U**

Or (C_1-C_6 alkylidene)-**L**-**U**

Or N-R^1R^2

Or The groups

;

Or -E-CH_2-OH, -E-O-CO(C_1-C_4 alkyl), -E-NH_2, -E-NH(C_1-C_4 alkyl), -E-N(C_1-C_4 alkyl)$_2$, -E-NH-CO(C_1-C_4 alkyl), -E-N(C_1-C_4 alkyl)-CO(C_1-C_4 alkyl), -E-(C_3-C_6 cycloalkyl), -E-CH_2-L-(C_1-C_4 alkyl), -E-CH_2-L-OH, -E-CH_2-L-O(C_1-C_4 alkyl), -E-CH_2-L-NH_2, -E-CH_2-L-NH(C_1-C_4 alkyl), -E-CH_2-L-N(C_1-C_4 alkyl)$_2$ or tetrazolyl;

And

E Represents a single bond, or an optionally branched C_1-C_4 alkylidene group;

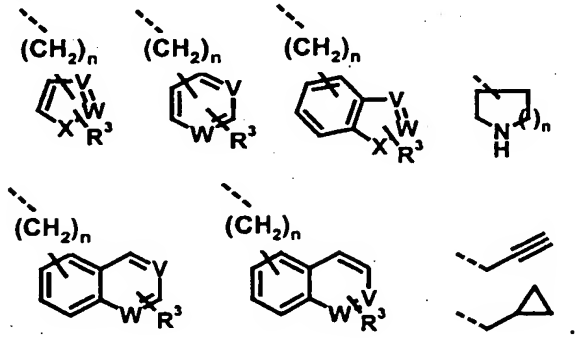
G Represents -O- or –NR^4-;

K Represents $(CH_2)_m$, with m = 0-6; optionally substituted with one group R^3 or an optionally branched C_3-C_6 alkyl group;

L Represents >C=O, >C=S, >C=NH, >S=O, or >SO_2;

M Represents -R^1, -OR^1, -SR^1, or –NR^1R^2;

Q Represents One of the groups



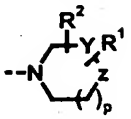
;

with n = 1, 2, 3;

T Represents -L or a group -CH(OH)-K, -CO-K;

U Represents -M;

Or a group



Y representing $-CH_2-$, and p = 0, 1, 2;

or with **Z** and **Y** combined representing a group -CH=CH-

and p = 0, 1;

V, W Represents >CH- or >N-;

X Represents -O-, -S-, or $>NR^1$;

Z Represents $-CH_2-$, $>N-R^1$, or a group >N-**L**-**M**;

With

R^1, R^2 Independently representing -H;

or an optionally branched C_1-C_6 alkyl-, alkenyl-, or alkinyl group, a C_0-C_3-alkyliden-C_3-C_6-cycloalkyl group, or a C_1-C_6 alkoxy group, optionally substituted with R^3;

or a C_0-C_3 alkyliden aryl group, optionally substituted with R^3;

or a C_0-C_3 alkyliden heteroaryl or C_0-C_3 alkyliden heterocycloalkyl group optionally interrupted by one ore more N-, O- and/or S-atoms and/or interrupted by one ore more C=O, SO SO_2 groups, the ring optionally substituted with R^3;

with the proviso, that between two of the above mentioned substituents, when attached to a single nitrogen, a single or double bond can be formed, resulting together with the nitrogen in an 3-7 membered heterocycloalkyl- or hetero-cycloalkenyl ring, optionally interrupted by one ore more N-, O- and/or S-atoms and/or interrupted by one ore more C=O, SO SO_2 groups, the ring optionally substituted with R^3;or a five membered heteroaromatic ring with up to three heteroatoms selected from O, S, N or a six membered heteroaromatic ring with one to three nitrogen atoms, optionally substituted with R^3,

while each of the ringsystems, mentioned in the description of R1 and R2 are optionally benzocondensed,

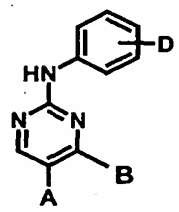
R^3 Representing up to three groups independently selected from

-H, -F, -Cl, -Br, -I, -CN, $-NO_2$, **-E-OH**, **-E-O-CO**(C_1-C_4 alkyl), **-E-NH_2**, **-E-NH**(C_1-C_4 alkyl), **-E-N**(C_1-C_4 alkyl)$_2$, **-E-NH-CO**(C_1-C_4 alkyl), **-E-N**(C_1-C_4 alkyl)**-CO**(C_1-C_4 alkyl), **-E-**(C_3-C_6 cycloalkyl), **-E-L-**(C_1-C_4 alkyl), **-E-L-OH**, **-E-L-O**(C_1-C_4 alkyl), **-E-L-NH_2**, **-E-L-NH**(C_1-C_4 alkyl), **-E-L-N**(C_1-C_4 alkyl)$_2$, an optionally branched C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or tetrazolyl;

R^4 Representing -H, or an optionally branched C_1-C_6 alkyl;

and all related isotopes, isomers, and pharmacologically acceptable salts thereof.

2. Compounds of general structure **(II)**,



(II)

wherein

A Represents -F, -Cl, -Br, -I, -CN, $-NO_2$, $-CF_3$, CH_3, $-CH_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, or an optionally branched C_3-C_6 alkyl, alkenyl, or alkinyl group, or a C_3-C_6 cycloalkyl group, or an optionally branched C_1-C_3 alkoxy group;

B Represents **-G-**(C_2-C_6 alkylidene)**-G-L-M**;

D Represents up to three substituents indepedently chosen from

H

Or **-R^3**;

Or **-K-U**;

or **-K-L-U**;

or **-K-G-K-T-U**;

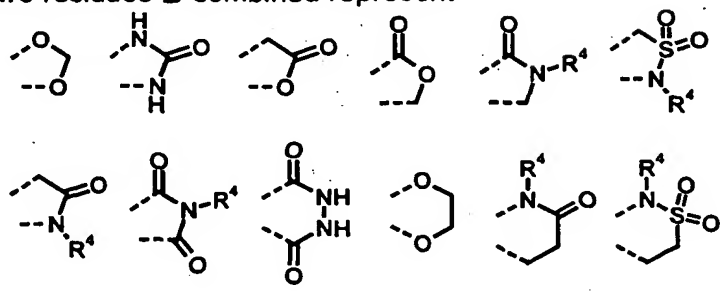
With the proviso, that between two of the above mentioned substituents, when attached to adjactent carbon atoms, a single bond can be formed, resulting together with the two carbons of the adjactend phenyl ring in a five membered heteroaromatic ring with up to three heteroatoms selected from O, S, N or a six membered heteroaromatic ring with one to three nitrogen atoms, whereby the resulting bicyclic ringsystem is optionally substituted with **R^3**;

or The groups

;

Or Two residues **D** combined represent

;



And

E Represents a single bond, or an optionally branched C_1-C_4 alkylidene group;

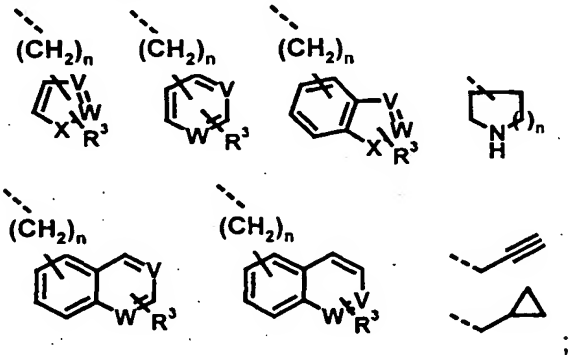
G Represents -O- or $-NR^4$-;

K Represents $(CH_2)_m$, with m = 0-6; ; optionally substituted with one group R^3 or an optionally branched C_3-C_6 alkyl group;

L Represents >C=O, >C=S, >C=NH, >S=O, or $>SO_2$;

M Represents $-R^1$, $-OR^1$, $-SR^1$, or $-NR^1R^2$;

Q Represents one of the groups



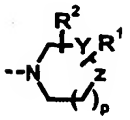
;

with n = 1, 2, 3;

T Represents -L or a group -CH(OH)-K, -CO-K;

U Represents **-M**;

Or a group



Y representing $-CH_2-$, and p = 0, 1, 2;

or with **Z** and **Y** combined representing a group -CH=CH-

and p = 0, 1;

V, W Represents >CH- or >N-;

X Represents -O-, -S-, or >N**R**^{1};

Z Represents $-CH_2-$, >N-**R**^{1}, or a group >N-**L**-**M**;

With

R^1, **R**^{2} Independently representing -H;

or an optionally branched C_1-C_6 alkyl-, alkenyl-, or alkinyl group, a C_0-C_3-alkyliden-C_3-C_6-cycloalkyl group, or a C_1-C_6 alkoxy group, optionally substituted with **R**^{3};

or a C_0-C_3 alkyliden aryl group, optionally substituted with **R**^{3};

or a C_0-C_3 alkyliden heteroaryl or C_0-C_3 alkyliden heterocycloalkyl group optionally interrupted by one ore more N-, O- and/or S-atoms and/or interrupted by one ore more C=O, SO SO_2 groups, the ring optionally substituted with **R**^{3};

with the proviso, that between two of the above mentioned substituents, when attached to a single nitrogen, a single or double bond can be formed, resulting together with the nitrogen in an 3-7 membered heterocycloalkyl- or heterocycloalkenyl ring, optionally interrupted by one ore more N-, O- and/or S-atoms and/or interrupted by one ore more C=O, SO SO_2 groups, the ring optionally substituted with **R**^{3};or a five membered heteroaromatic ring with up to three heteroatoms selected from O, S, N or a six membered heteroaromatic ring with one to three nitrogen atoms, optionally substituted with R^3,

while each of the ringsystems, mentioned in the description of R1 and R2 are optionally benzocondensed,

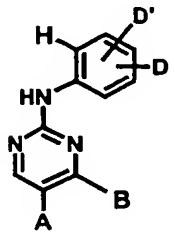
R^3 Representing up to three groups independently selected from

-H, -F, -Cl, -Br, -I, -CN, $-NO_2$, -E-OH, -E-O-CO(C_1-C_4 alkyl), -E-NH_2, -E-NH(C_1-C_4 alkyl), -E-N(C_1-C_4 alkyl)$_2$, -E-NH-CO(C_1-C_4 alkyl), -E-N(C_1-C_4 alkyl)-CO(C_1-C_4 alkyl), -E-(C_3-C_6 cycloalkyl), -E-L-(C_1-C_4 alkyl), -E-L-OH, -E-L-O(C_1-C_4 alkyl), -E-L-NH_2, -E-L-NH(C_1-C_4 alkyl), -E-L-N(C_1-C_4 alkyl)$_2$, an optionally branched C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or tetrazolyl;

R^4 Representing -H, or an optionally branched C_1-C_6 alkyl;

and all related isotopes, isomers, and pharmacologically acceptable salts thereof.

3. Compounds of general structure **(III)**,



(III)

wherein

A Represents -F, -Cl, -Br, $-CF_3$, CH_3, $-C_2H_5$, $-O-CH_3$, or $-O-C_2H_5$;

B Represents a group **-G-K-Q**;
or a group **-G-K-L-M**;
Or A group **–G-**(C_2-C_6 alkylidene)-**M**
or a group **-G-**(C_2-C_6 alkylidene)-**G-L-M**;

D Represents a substituent chosen from
-R³;

D' Represents $-NH-CO-NR^1R^2$
or 

Or $-O-CH_2-CH(OH)-CH_2-$**U'**
Or $-O-CH_2-CO-CH_2-$**U'**

Or (C_0-C_3 alkylidene)-**U'**
Or **-G-**(C_1-C_3 alkylidene)-**CO-M**
Or **-G-**(C_1-C_3 alkylidene)-**G-**$CO-R^1$

And

E Represents A single bond, or an optionally branched C_1-C_2 alkylidene group;

G Represents -O- or $-NR^4-$;

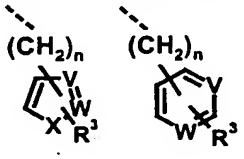
K Represents $(CH_2)_m$, with m = 0-5

or an optionally branched C_3-C_5 alkyl group, each of the mentioned groups optionally substituted with one group R^3

L Represents >C=O or $>SO_2$;

M Represents $-R^1$, $-OR^1$ or $-NR^1R^2$;

Q Represents One of the groups



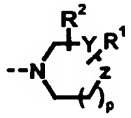
;

with n = 1, 2, 3;

T Represents **-L** or a group -CH(OH)-**K**, -CO-**K**;

U Represents **-M**;

Or a group



Y representing $-CH_2-$, and p = 0, 1, 2;

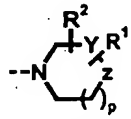
or with **Z** and **Y** combined representing a group -CH=CH-

and p = 0, 1;

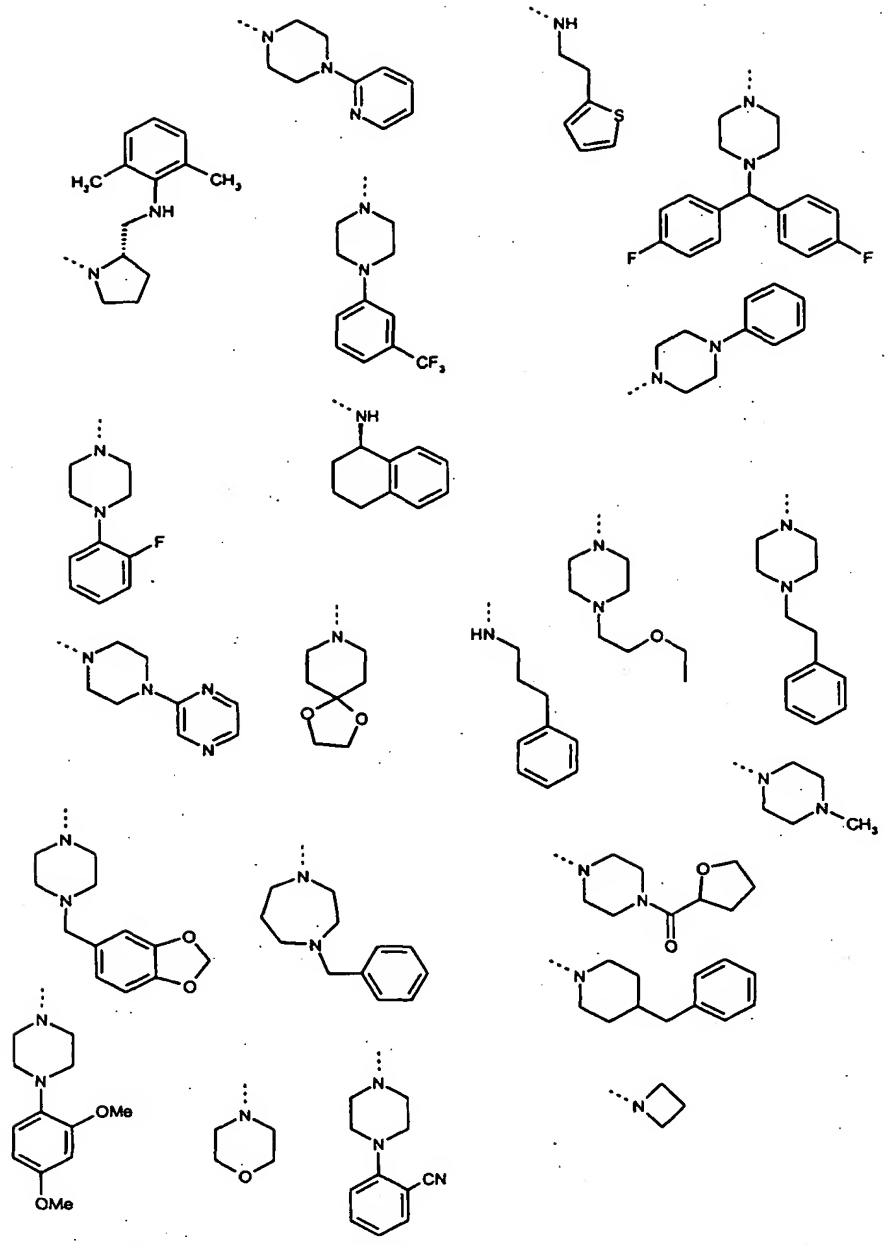
U' Represents $-NR^1R^2$

Or R^1

or



except the following residues:



V, W Represents >CH- or >N-;

X Represents -O-, -S-, or >N**R**[1];

Z Represents -CH_2-, >N-**R**[1], or a group >N-L-**M**;

With

R^1, R^2 Independently representing -H;

Or an optionally branched C_1-C_6 alkyl-, alkenyl-, or alkinyl group, a C_0-C_3-alkyliden-C_3-C_6-cycloalkyl group, or a C_1-C_6 alkoxy group, optionally substituted with **R^3**;

Or a C_0-C_3 alkyliden aryl group, optionally substituted with **R^3**;

or a C_0-C_3 alkyliden heteroaryl or C_0-C_3 alkyliden heterocycloalkyl group optionally interrupted by one ore more N-, O- and/or S-atoms and/or interrupted by one ore more C=O, SO SO_2 groups, the ring optionally substituted with **R^3**;

with the proviso, that between two of the above mentioned substituents, when attached to a single nitrogen, a single or double bond can be formed, resulting together with the nitrogen in an 3-7 membered heterocycloalkyl- or hetero-cycloalkenyl ring, optionally interrupted by one ore more N-, O- and/or S-atoms and/or interrupted by one ore more C=O, SO SO_2 groups, the ring optionally substituted with **R^3**;or a five membered heteroaromatic ring with up to three heteroatoms selected from O, S, N or a six membered heteroaromatic ring with one to three nitrogen atoms, optionally substituted with R^3,

while each of the ringsystems, mentioned in the description of R1 and R2 are optionally benzocondensed,

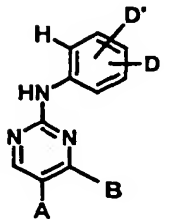
R^3 Representing up to three groups independently selected from

-H, -F, -Cl, -Br, -I, -CN, -NO_2, -**E**-OH, -**E**-O-CO(C_1-C_4 alkyl), -**E**-NH_2, -**E**-NH(C_1-C_4 alkyl), -**E**-N(C_1-C_4 alkyl)$_2$, -**E**-NH-CO(C_1-C_4 alkyl), -**E**-N(C_1-C_4 alkyl)-CO(C_1-C_4 alkyl), -**E**-(C_3-C_6 cycloalkyl), -**E**-**L**-(C_1-C_4 alkyl), -**E**-**L**-OH, -**E**-**L**-O(C_1-C_4 alkyl), -**E**-**L**-NH_2, -**E**-**L**-NH(C_1-C_4 alkyl), -**E**-L-N(C_1-C_4 alkyl)$_2$, an optionally branched C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or tetrazolyl;

R^4 Representing -H, or an optionally branched C_1-C_6 alkyl;

and all related isotopes, isomers, and pharmacologically acceptable salts thereof.

4. Compounds of general structure (IV),

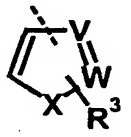


(IV)

wherein

A Represents -Cl, -Br, -I, $-CH_3$, $-OCH_3$

B Represents a group **-G-K-Q**; wherein **G** is **$-NR^4-$** and **R^4** is defined herein,

K is $(CH_2)_m$ with m = 2 or 3, and **Q** is 

where **V** is **>N-**; **W** is **>CH--**; and **R^3** is defined herein.

Or a group **-G-K-M**; wherein **G** is **$-NR^4-$** and **R^4** is defined herein, **K** is $(CH_2)_m$ with m = 3, 4 or 5, and **M** is **$-NR^1R^2$** where **R^1** and **R^2** are –H.

Or a group **–G-**(C_3-C_5 alkylene)**-G-L-M**; wherein **G** is **$-NR^4-$** and **R^4** as defined herein; **L** is >C=O; and **M** is $-NR^1R^2$ or R^1

D Represents -H, -F, -Cl, -Br, -I, -CN, $-NO_2$, **-E-OH**, **-E-O-CO**(C_1-C_4 alkyl), **-E-NH**$_2$, **-E-NH**(C_1-C_4 alkyl), **-E-N**(C_1-C_4 alkyl)$_2$, **-E-NH-CO**(C_1-C_4 alkyl), **-E-N**(C_1-C_4 alkyl)**-CO**(C_1-C_4 alkyl), **-E-**(C_3-C_6 cycloalkyl), **-E-L-**(C_1-C_4 alkyl), **-E-L-OH**, **-E-L-O**(C_1-C_4 alkyl), **-E-L-NH**$_2$, **-E-L-NH**(C_1-C_4 alkyl), **-E-L-N**(C_1-C_4 alkyl)$_2$, an optionally branched C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, or tetrazolyl;

D' Represents a group -**K-G-K-T-U**; wherein **K** is $(CH_2)_m$ with m = 0-1, **G** is –NR^4-, and R^4 is defined herein; **K** is $(CH_2)_m$ with m = 0, **T** is >C=O, and **U** is $-NR^1R^2$

and all related isotopes, isomers and pharmacologically acceptable salts thereof.

5. A pharmaceutical composition comprising as an active ingredient at least one compound as defined in any one of claims 1-4 together with pharmaceutically acceptable carriers, diluents and/or adjuvants.

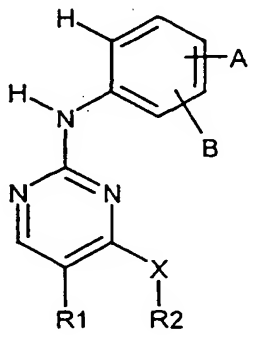
6. The use of a compound of any one of claims 1-4 for the manufacture of a medicament for the prevention or treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation.

7. The use of a compound of any one of claims 1-4 for the manufacture of a medicament for the prevention or treatment of a disorder caused by, associated with or accompanied by an abnormal kinase activity selected from Chk, Akt, Pdk and Cdk activity as well as combinations thereof.

8. The use of claim 7, wherein the kinase is Chk1 and/or Chk2.

9. The use of claim 7, wherein the kinase is Pdk1, Akt1, Akt2 and/or Akt3.

10. Use of Compounds of general formula (V)



(V)

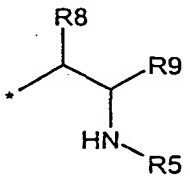
in which

R^1 stands for hydrogen, halogen, C_1-C_6-alkyl, nitro, or for the group $-COR^5$, $-OCF_3$, $-(CH_2)_nR^5$, $-S-CF_3$ or $-SO_2CF_3$,

R^2 stands for C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkinyl, or C_3-C_{10}-cycloalkyl or for C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkinyl, or C_3-C_{10}-cycloalkyl that is substituted in one or more places in the same way or differently with hydroxy, halogen, C_1-C_6-alkoxy, C_1-C_6-alkylthio, amino, cyano, C_1-C_6-alkyl, $-NH(CH_2)n-C_3$-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl, C_1-C_6-hydroxyalkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, $-NHC_1$–C_6–alkyl, $-N(C_1$-C_6-alkyl)$_2$, $-SO(C_1$-C_6-alkyl), $-SO_2(C_1$-C_6-alkyl), C_1-C_6-alkanoyl, $-CONR^3R^4$, $-COR^5$, C_1-C_6-alkylOAc, carboxy, aryl, heteroaryl, $-(CH_2)_n$-aryl, $-(CH_2)_n$-heteroaryl, phenyl-$(CH_2)_n$-R^5, $-(CH_2)_nPO_3(R^5)_2$ or with the group $–R^6$ or $–NR^3R^4$, and the phenyl, C_3-C_{10}-cycloalkyl, aryl, heteroaryl, and $-(CH_2)_n$-aryl itself optionally can be substituted in one or

more places in the same way or differently with halogen, hydroxy, C_1-C_6-alkyl, C_1–C_6-alkoxy, heteroaryl, benzoxy, or with the group $-CF_3$ or $-OCF_3$, and the ring of the C_3–C_{10}–cycloalkyl C_1–C_{10}–alkyl optionally can be interrupted by one or more nitrogen, oxygen and/or sulfur atoms and/or can be interrupted by one or more =C=O groups in the ring and/or optionally one or more possible double bonds can be contained in the ring, or

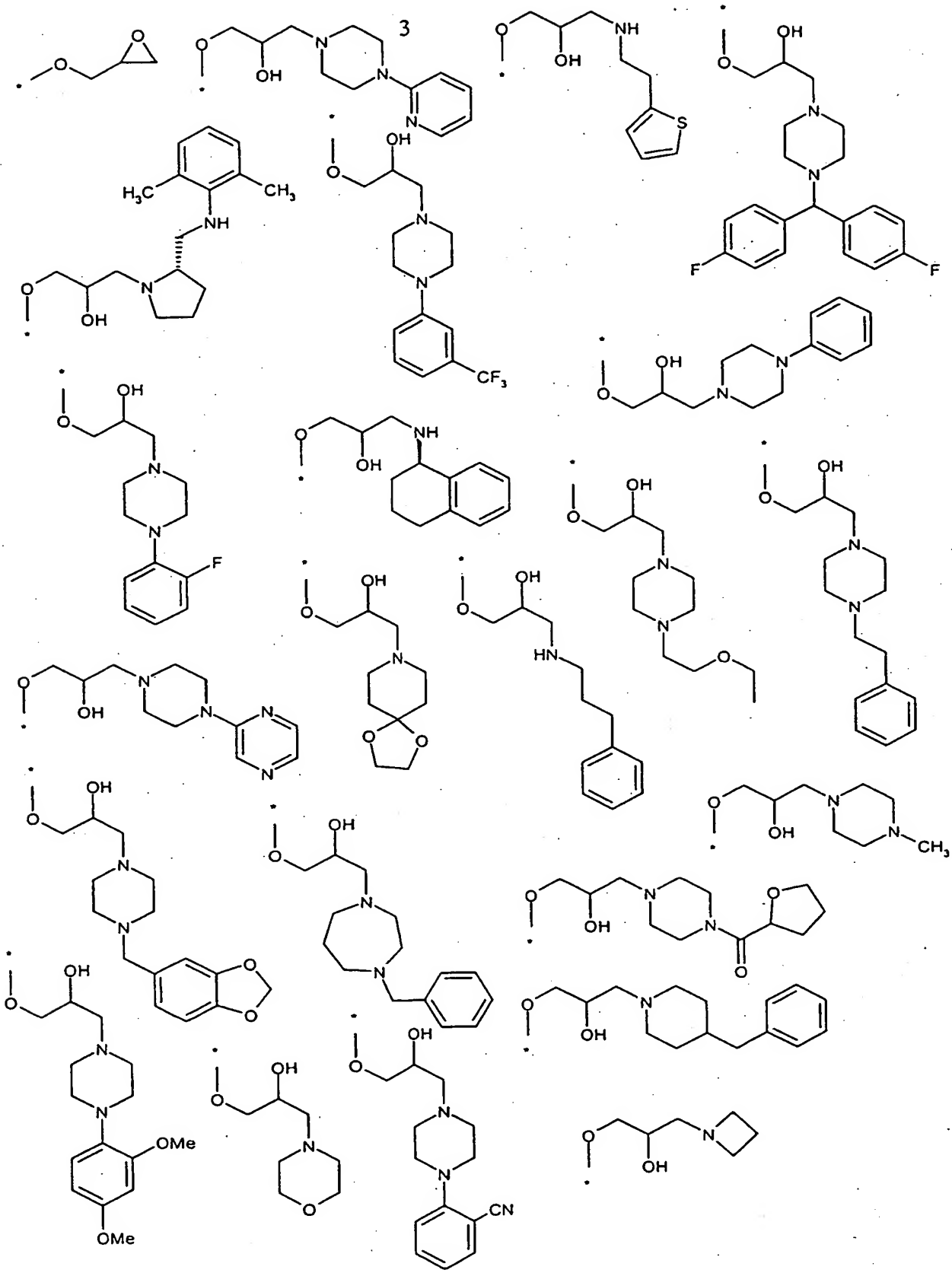
R^2 stands for the group



X stands for oxygen or for the group –NH-, -N(C_1-C_3-alkyl)-, or for –OC_3-C_{10}-cycloalkyl, which can be substituted in one or more places in the same way or differently with a heteroaromatic compound, or

X and R^2 together form a C_3-C_{10}-cycloalkyl ring, which optionally can contain one or more heteroatoms and optionally can be substituted in one or more places with hydroxy, C_1-C_6-alkyl, C_1-C_6-alkoxy or halogen,

A and B, in each case independently of one another, stand for hydrogen, hydroxy, C_1-C_3-alkyl, C_1-C_6-alkoxy or for the group $-SR^7$, $-NHSO_2R^7$, $-CH(OH)R^7$, $-CR^7(OH)-R^7$, or $-COR^7$, or for



or

A and B together form a C_3–C_{10}–cycloalkyl ring that optionally can be interrupted by one or more nitrogen, oxygen and/or sulfur atoms and/or can be interrupted by one or more =C=O or $=SO_2$ groups in the ring and/or optionally one or more possible double bonds can be contained in the ring, and the C_3–C_{10}–cycloalkyl ring optionally can be substituted in one or more places in the same way or differently with hydroxy, halogen, C_1-C_6-alkoxy, C_1–C_6–alkylthio, amino, cyano, C_1–C_6–alkyl, C_2–C_6–alkenyl, C_3–C_{10}–cycloalkyl, C_1–C_6–alkoxy-C_1–C_6–alkyl, -NHC_1–C_6–alkyl, -$N(C_1$–C_6–alkyl$)_2$, -$SO(C_1$–C_6–alkyl), -SO_2R^7, C_1–C_6-alkanoyl, -$CONR^3R^4$, -COR^5, C_1–C_6–alkoxyOAc, phenyl or with the group R^6, whereby the phenyl itself optionally can be substituted in one or more places in the same way or differently with halogen, hydroxy, C_1–C_6-alkyl, C_1–C_6–alkoxy or with the group –CF_3 or -OCF_3,

R^3 and R^4, in each case independently of one another, stand for hydrogen, phenyl, benzyloxy, C_1-C_{12}-alkyl, C_1-C_6-alkoxy, C_2-C_4-alkenyloxy, C_3-C_6-cycloalkyl, hydroxy, hydroxy-C_1–C_6–alkyl, dihydroxy-C_1–C_6–alkyl, heteroaryl, heterocyclo-C_3-C_{10}-alkyl, heteroaryl-C_1-C_3-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl that is optionally substituted with cyano, or for

C_1-C_6-alkyl that is optionally substituted in one or more places in the same way or differently with phenyl, pyridyl, phenyloxy, C_3-C_6-cycloalkyl, C_1-C_6-alkyl or C_1-C_6-alkoxy,

whereby the phenyl itself can be substituted in one or more places in the same way or differently with halogen, C_1-C_6-alkyl, C_1-C_6-alkoxy or with the group $-SO_2NR^3R^4$,

or for the group $-(CH_2)_nNR^3R^4$, $-CNHNH_2$ or $-NR^3R^4$

or

R^3 and R^4 together form a C_3-C_{10}–cycloalkyl ring that optionally can be interrupted by one or more nitrogen, oxygen and/or sulfur atoms and/or can be interrupted by one or more =C=O groups in the ring and/or optionally one or more possible double bonds can be contained in the ring,

R^5 stands for hydroxy, phenyl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, benzoxy, C_1-C_6-alkylthio or C_1-C_6-alkoxy,

R^6 stands for a C_3–C_{10}-cycloalkyl ring, whereby the ring has the above-indicated meaning,

R^7 stands for halogen, hydroxy, phenyl, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_3-C_{10}-cycloalkyl, with the above-indicated meaning, or for the group $-NR^3R^4$, or for C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkinyl or C_3-C_7-cycloalkyl that is substituted in one or more places in the same way or differently with hydroxy, C_1-C_6-alkoxy, halogen, phenyl, $-NR^3R^4$ or phenyl, which itself can be substituted in one or more places in the same way or differently with halogen, hydroxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or R^7 stands for phenyl, which itself can be substituted in one or more places in the same way or differently

with halogen, hydroxy, C_1-C_6-alkyl or C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, or halo-C_1-C_6-alkoxy,

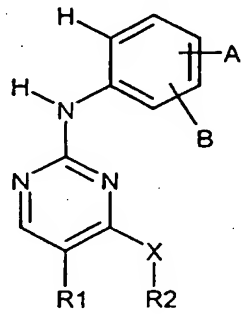
R^8 and R^9

in each case independently of one another, stands for hydrogen, hydroxy, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkinyl, C_3-C_{10}-cycloalkyl, aryl, heteroaryl, or for C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkinyl or C_3-C_{10}-cycloalkyl that is optionally substituted in one or more places in the same way or differently with hydroxy, halogen, C_1-C_6-alkoxy, C_1-C_6-alkylthio, amino, cyano, C_1-C_6-alkyl, -NH-$(CH_2)_n$-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl, C_1-C_6-hydroxyalkyl, C_2-C_6-alkenyl, C_2-C_6-alkinyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkoxy-C_1-C_6-alkyl, -NHC_1-C_6-alkyl, -N(C_1-C_6-alkyl)$_2$, –SO(C_1-C_6-alkyl), -SO_2(C_1-C_6-alkyl), C_1-C_6-alkanoyl, -$CONR^3R^4$, -COR^5, C_1-C_6-alkylOAc, carboxy, aryl, heteroaryl, -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl, phenyl-$(CH_2)_n$-R^5, -(CH_2)n$PO_3(R^5)_2$ or with the group –R^6 or –NR3R4, and the phenyl, C3-C10-cycloalkyl, aryl, heteroaryl, , -$(CH_2)_n$-aryl, -$(CH_2)_n$-heteroaryl itself optionally can be substituted in one or more places in the same way or differently with halogen, hydroxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, or with the group –CF_3 or –OCF_3, and the ring of C_3-C_{10}-cycloalkyl and the C_1-C_{10}-alkyl optionally can be interrupted by one or more nitrogen, oxygen and/or sulfur atoms and/or can be interrupted by one or more =C=O groups in the ring and/or optionally one or more possible double bonds can be contained in the ring, and

n stands for 0-6,

as well as isomers, diastereomers, enantiomers and salts thereof for the manufacture of a medicment for the prevention or treatment of a disorder caused by, associated with or accompanied by an abnormal kinase activity selected from Chk, Akt and Pdk activity as well as combinations thereof.

11. Use of compounds of general formula (VI)



in which

R^1 stands for hydrogen, halogen, C_1-C_2-alkyl

R^2 for C_2-C_5-alkyl or C_3-C_6-cycloalkyl that is substituted in one or more places in the same way or differently with C_1-C_6-alkoxy, amino, C_1-C_4-alkyl, C_3-C_7-cycloalkyl, C_1-C_4-hydroxyalkyl, -NHC_1–C_6–alkyl, -$N(C_1$-C_6-alkyl$)_2$, C_1-C_6-alkanoyl, -$CONR^3R^4$, -COR^5, heteroaryl, -$(CH_2)_n$-heteroaryl or with the group –NR^3R^4, and the C_3-C_6-cycloalkyl and heteroaryl itself optionally can be substituted in one or more places in the same way or differently with halogen, hydroxy, C_1-C_6-alkyl, C_1 –C_6-alkoxy, heteroaryl, or with the group –CF_3 or -OCF_3, and the ring of the C_3 –C_6 –cycloalkyl optionally can be interrupted by one or more nitrogen, oxygen and/or sulfur atoms and/or can be interrupted by one or more =C=O groups in the ring and/or optionally one or more possible double bonds can be contained in the ring,

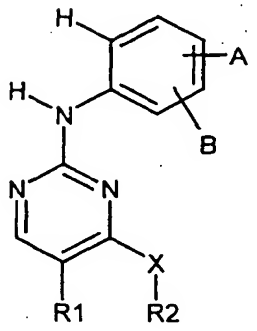
X stands for oxygen or for the group –NH- or -N(C_1-C_3-alkyl)-

A stand for the group -$NHSO_2R^7$ or –COR^7

B stands for hydrogen, hydroxy, C_1-C_3-alkyl, C_1-C_6-alkoxy or for the group –SR^7, -$NHSO_2R^7$, -$CH(OH)R^7$, -$CR^7(OH)$-R^7, or –COR^7

for the manufacture of a medicament for the prevention or treatment of a disorder caused by, associated with or accompanied by an abnormal kinase activity selected from Akt and/or Pdk activity.

12. Use of compounds of general formula (VII)



(VII)

in which

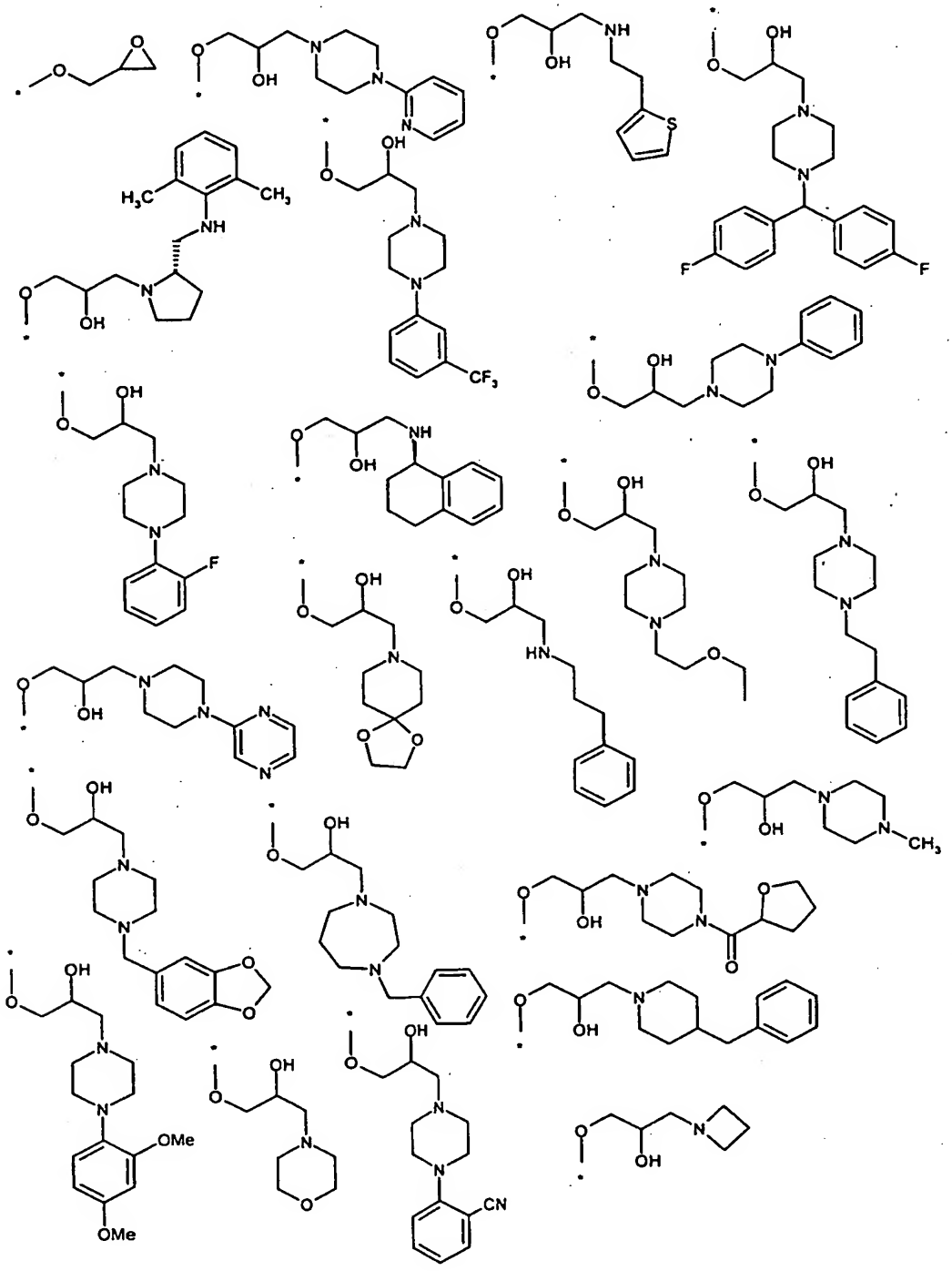
R^1 stands for hydrogen, halogen, C_1-C_3 -alkyl, or for the group -COR^5, -OCF_3 , -$(CH_2)_nR^5$,

R^2 stands for C_1-C_5-alkyl, C_2-C_5-alkenyl, C_2-C_5-alkinyl, or C_3-C_6-cycloalkyl or for C_1-C_5-alkyl, C_2-C_5-alkenyl, C_2-C_5-alkinyl, or C_3-C_6-cycloalkyl that is substituted in one or two places in the same way or differently with hydroxy, halogen, C_1-C_3 -alkoxy, amino, C_1-C_3-alkyl, -$NH(CH_2)$n-C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl, C_1-C_3-hydroxyalkyl, C_2-C_5 -alkenyl, C_2-C_5 -alkinyl, -NHC_1–C_3–alkyl, -$N(C_1$-C_3-alkyl$)_2$, C_1-C_4-alkanoyl, -$CONR^3R^4$, -COR^5, C_1-C_3-alkylOAc, carboxy, aryl, heteroaryl, phenyl-$(CH_2)_n$-R^5, or –NR^3R^4, and the phenyl, C_3-C_{10}-cycloalkyl, aryl, and heteroaryl itself optionally can be substituted in one to three places in the same way or differently with halogen, hydroxy, C_1-C_3-alkyl, C_1 –C_3-alkoxy, –CF_3 or -OCF_3 , and the ring of the C_3 –C_6 –cycloalkyl C_1 –C_3 – alkyl optionally can be interrupted by one or two nitrogen, oxygen and/or

sulfur atoms and/or can be interrupted by one or two =C=O groups in the ring and/or optionally one or more possible double bonds can be contained in the ring,

X stands for oxygen or for the group –NH-, -N(C_1-C_3-alkyl)-,

A represents one of the following groups



B stands for hydrogen, hydroxy, C_1-C_3-alkyl, C_1-C_4-alkoxy or for the group

$-SR^7$, $-NHSO_2R^7$, $-CH(OH)R^7$, $-CR^7(OH)-R^7$, or $-COR^7$,

R^3 and R^4, in each case independently of one another, stand for hydrogen, phenyl, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, hydroxy, hydroxy-C_1–C_4–alkyl, heteroaryl, heterocyclo-C_3-C_6-alkyl, heteroaryl-C_1-C_3-alkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, or for C_1-C_4-alkyl that is optionally substituted in one or two places in the same way or differently with phenyl, pyridyl, C_3-C_6-cycloalkyl, or C_1-C_3-alkoxy, whereby the phenyl itself can be substituted in one to three places in the same way or differently with halogen, C_1-C_6-alkyl, C_1-C_6-alkoxy or with the group $-SO_2NR^3R^4$, or for the group $-(CH_2)_nNR^3R^4$,

R^5 stands for hydroxy, C_1-C_3-alkyl, C_3-C_6-cycloalkyl, C_1-C_3-alkylthio or C_1-C_3-alkoxy,

R^6 stands for a C_3–C_6-cycloalkyl ring, whereby the ring has the above-indicated meaning,

R^7 stands for hydroxy, phenyl, C_1-C_3-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl, C_3-C_7-cycloalkyl, with the above-indicated meaning, or for the group $-NR^3R^4$, or for C_1-C_3-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkinyl or C_3-C_7-cycloalkyl that is substituted in one or two places in the same way or differently with hydroxy, C_1-C_3-alkoxy, phenyl, $-NR^3R^4$ or phenyl, which itself can be substituted in one to three places in the same way or differently with halogen, hydroxy, C_1-C_3-alkyl, C_1-C_3-alkoxy, or R^7 stands for phenyl, which itself can be substituted in one to three places in the

same way or differently with halogen, hydroxy, C_1-C_3-alkyl or C_1-C_3-alkoxy,

n stands for 0-3,

as well as isomers, diastereomers, enantiomers and salts thereof for the manufacture of a medicament for the prevention or treatment of a disorder caused by, associated with or accompanied by an abnormal kinase activity selected from Chk activity.

13. The use according to any one of claims 6-12, wherein the disorder is selected from cancer, auto-immune diseases, chemotherapy agent-induced alopecia and mucositis, cardiovascular diseases, infectious diseases, nephrological diseases, chronic and acute neurodegenerative diseases and viral infections.

14. The use according to claim 13, wherein cancer is defined as solid tumors and leukemia; auto-immune diseases are defined as psoriasis, alopecia and multiple sclerosis; cardiovascular diseases are defined as stenoses, arterioscleroses and restenoses; infectious diseases are defined as diseases that are caused by unicellular parasites; nephrological diseases are defined as glomerulonephritis; chronic neurodegenerative diseases are defined as Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease, AIDS dementia and Alzheimer's disease; acute neurodegenerative diseases are defined as ischemias of the brain and neurotraumas; and viral infections are defined as cytomegalic infections, herpes, hepatitis B and C, and HIV diseases.

15. The use of any one of claims 6-14, wherein the compounds of are in the form of a pharmaceutical preparation for enteral, parenteral or oral administration.

16. Use of the compounds of general formulae I-VII as inhibitors of the Akt, Chk and/or Pdk kinases.

Abstract

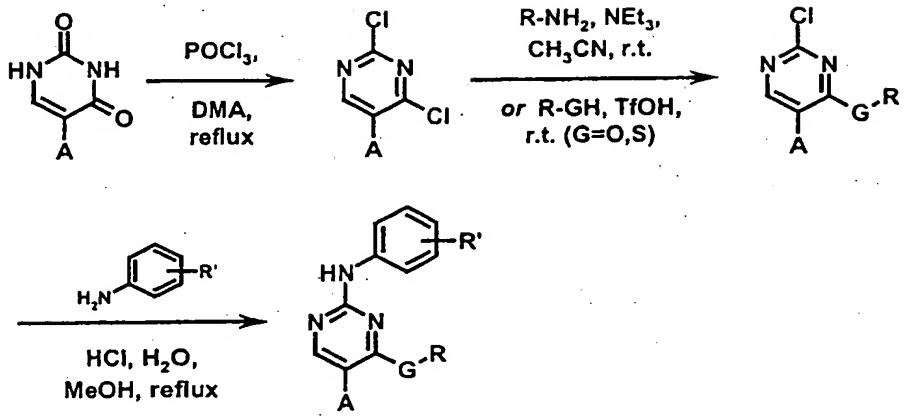
This invention relates to pyrimidine derivatives as inhibitors of kinases, their production as well as their use as medications for treating various diseases.

Id 28.11.2002

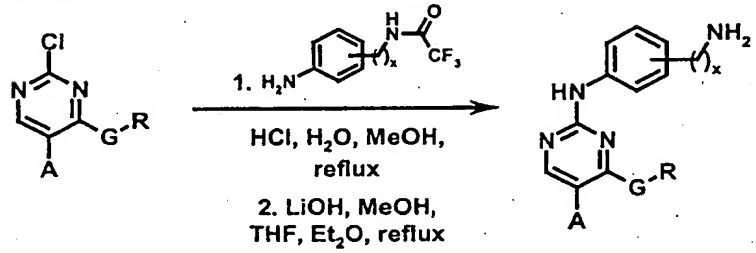
Figure 1

B. Synthetic Schemes

Scheme 1:



Scheme 2:



Scheme 3:

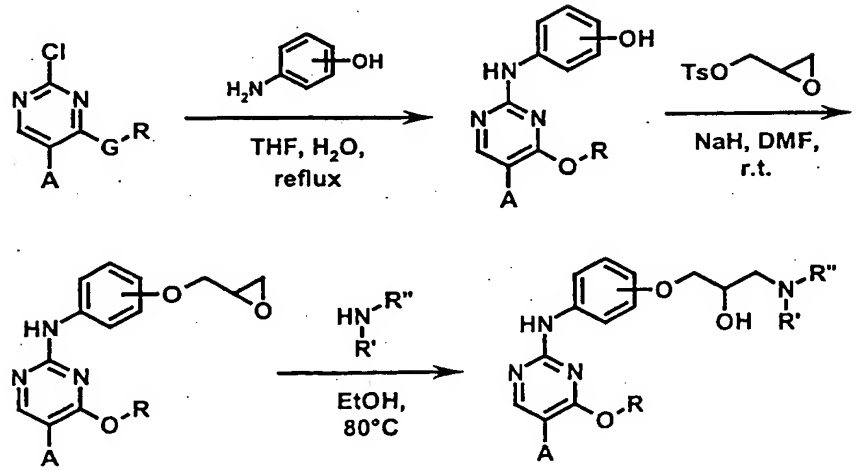
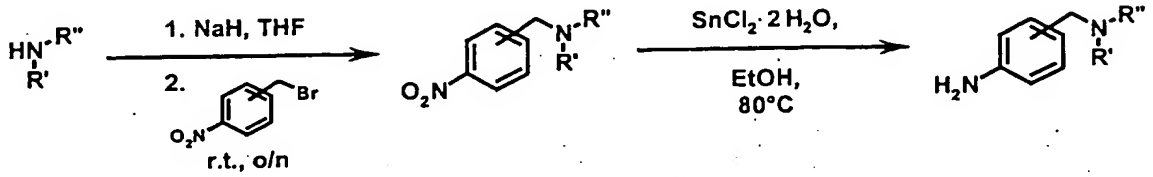


Figure 1 (cont.)

Scheme 4:



Scheme 5:

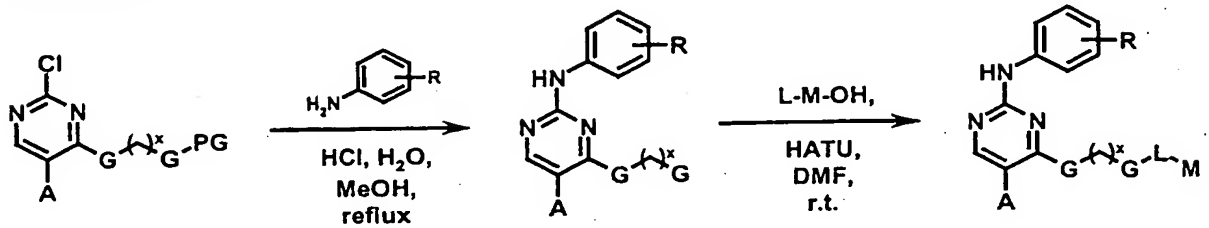
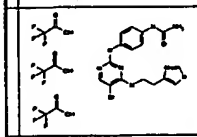
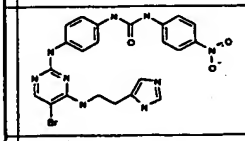
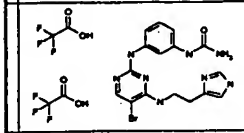
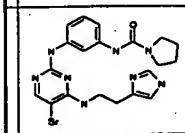
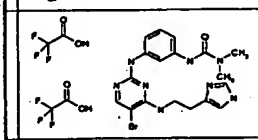
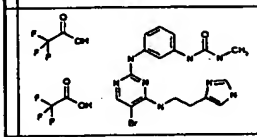
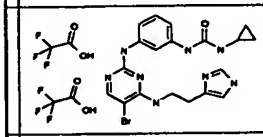
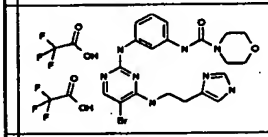
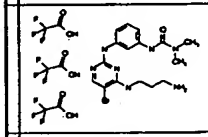
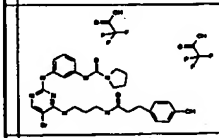
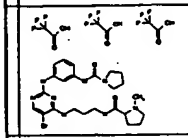
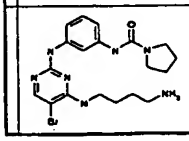
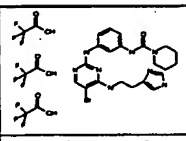
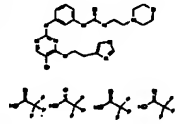
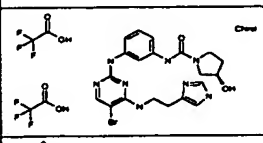
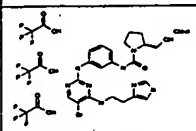
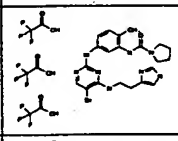
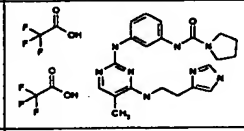
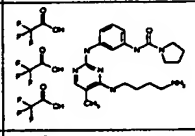
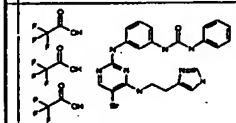
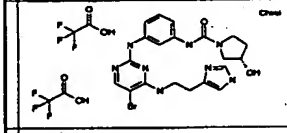
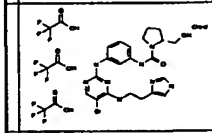
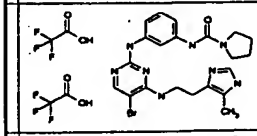
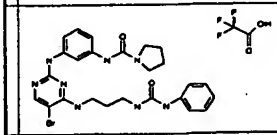
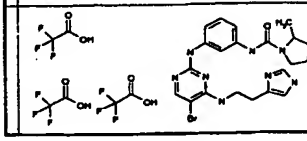
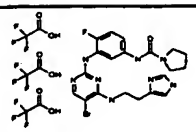
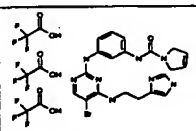
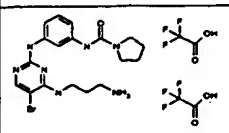
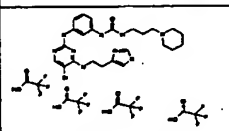
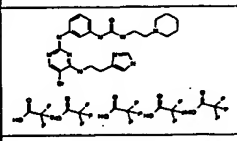
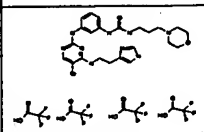
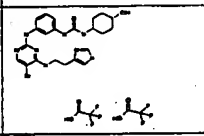
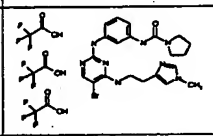
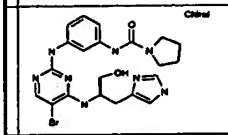
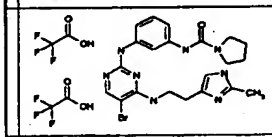
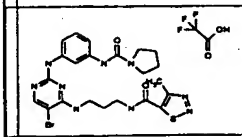
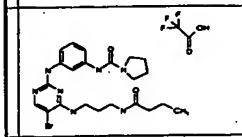
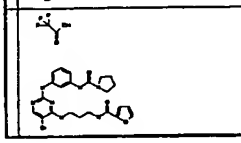


Fig. 2/1

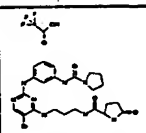
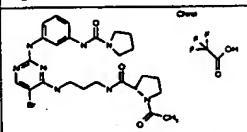
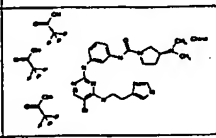
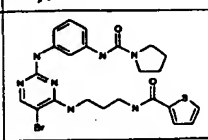
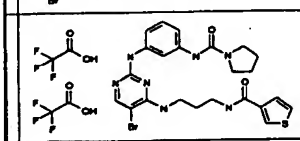
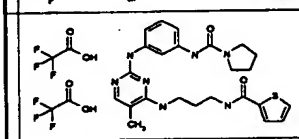
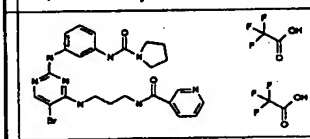
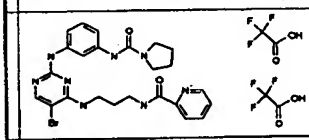
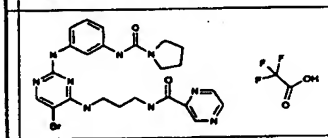
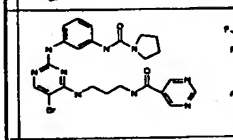
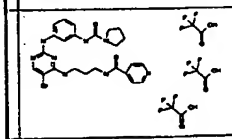
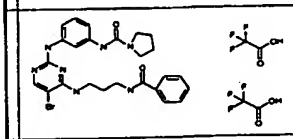
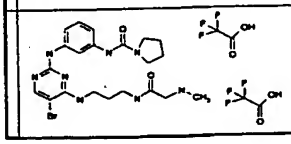
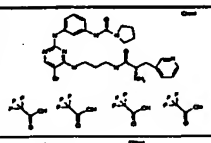
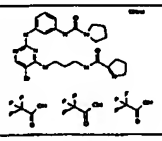
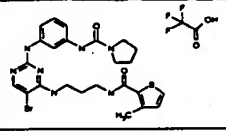
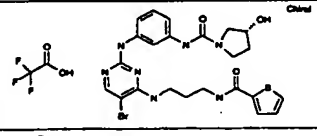
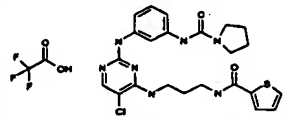
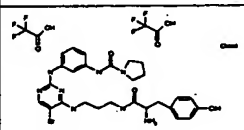
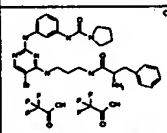
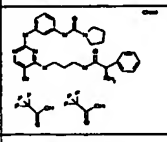
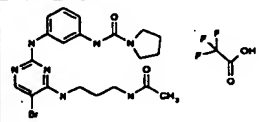
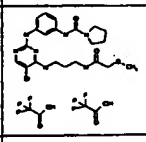
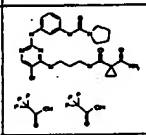
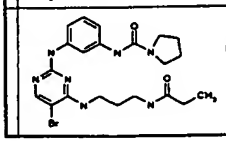
	
	
	
	
	
	
	
	
	
	
	
	
	

Fig. 2/5

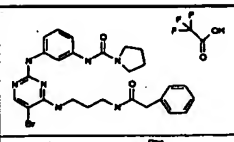
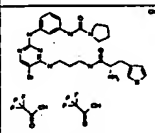
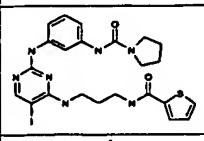
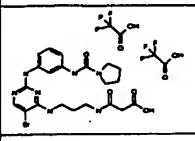
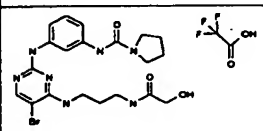
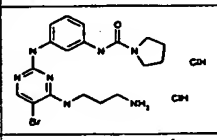
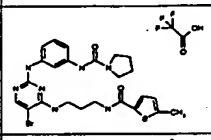
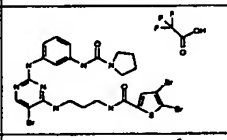
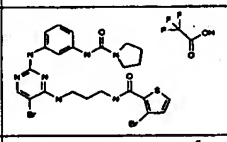
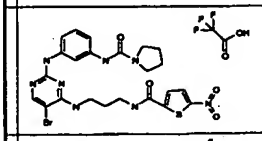
	
	
	
	
	
	
	
	
	
	

Figure 3

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	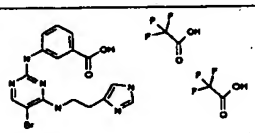
	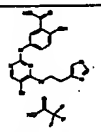
	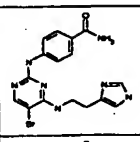
	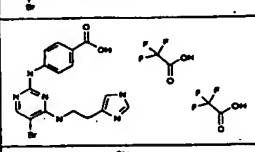
	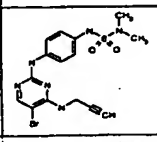
	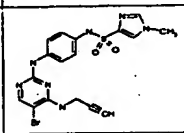
	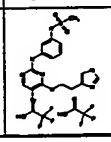

Figure 4

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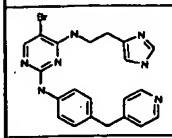
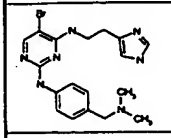
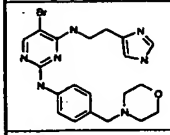
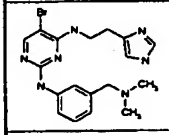
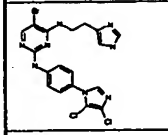
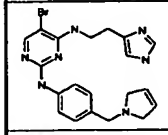
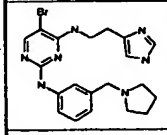
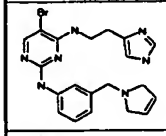
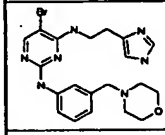
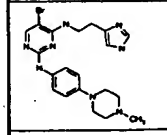
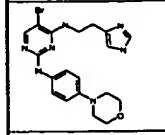
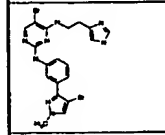
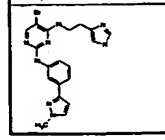

Figure 5

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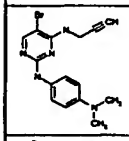
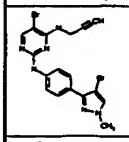
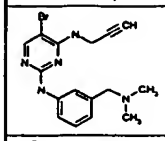
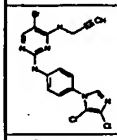
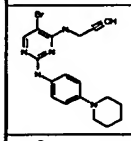
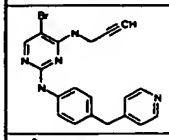
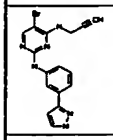
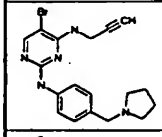
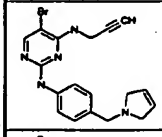
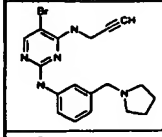
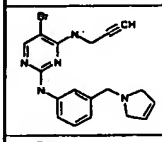
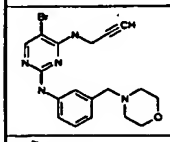
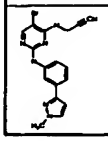

Fig. 6/1

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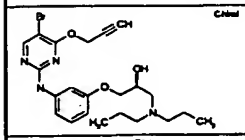
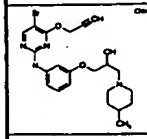
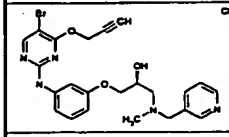
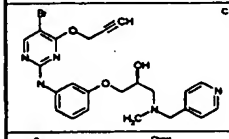
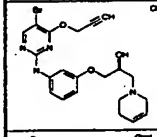
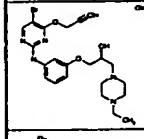
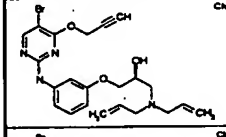
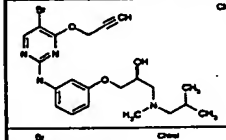
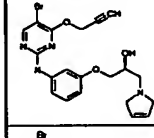
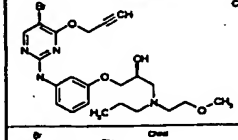
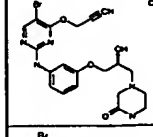
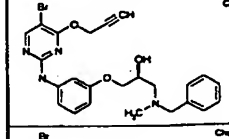
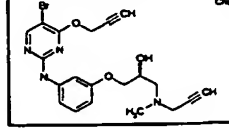

Fig. 6/2

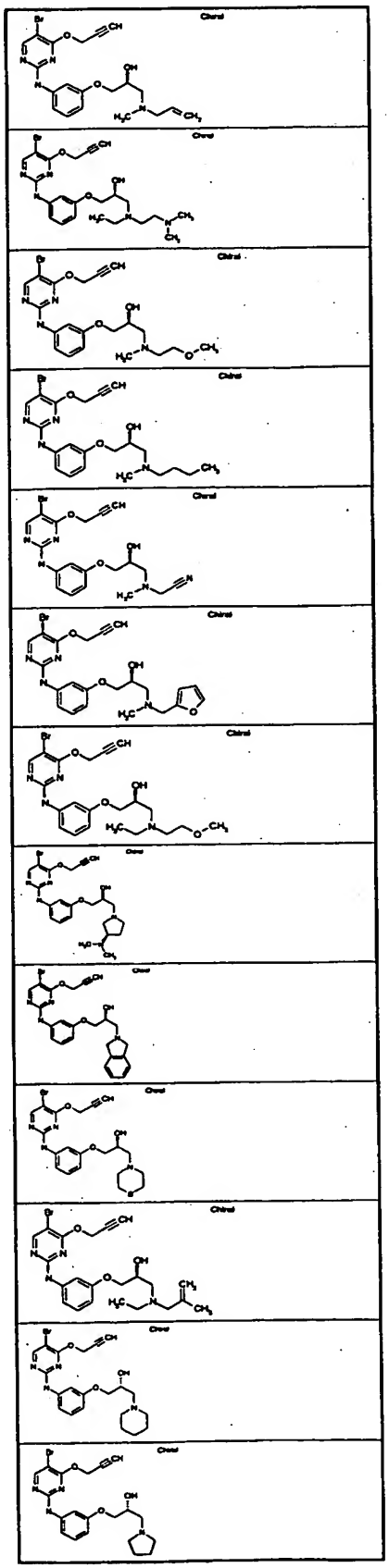

Fig. 6/3

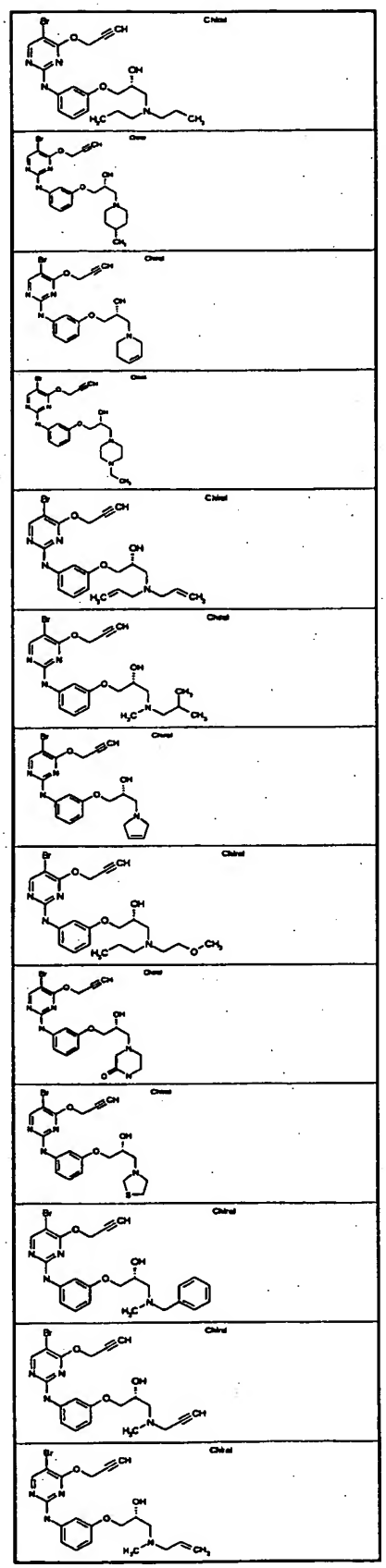

Fig. 6/4

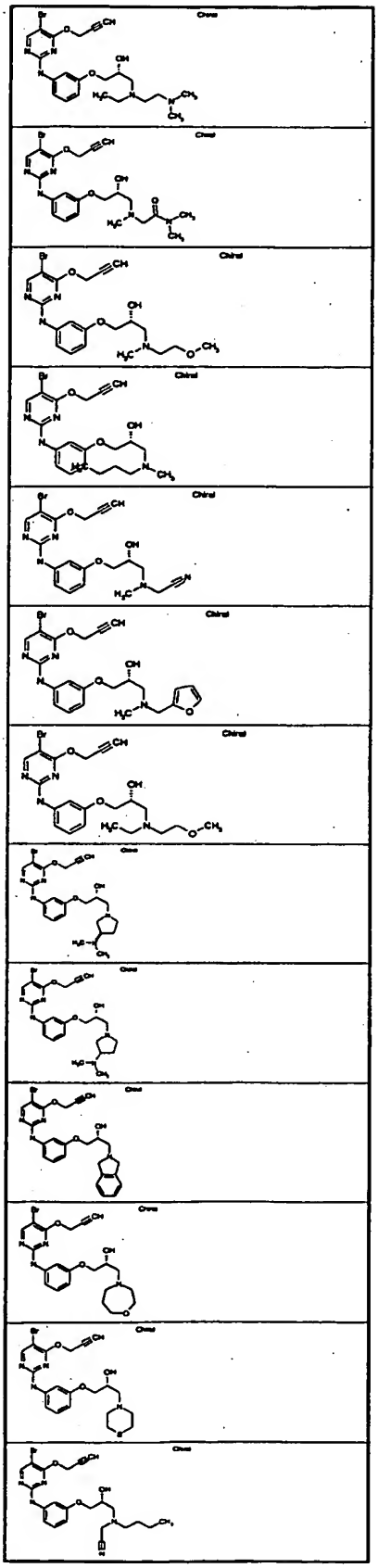

Fig. 6/5

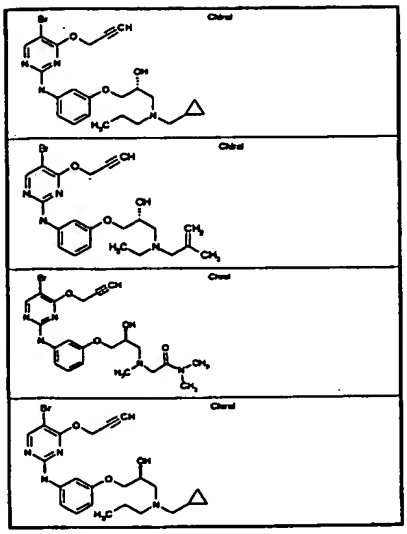

Fig. 7/1

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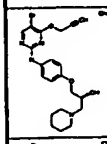
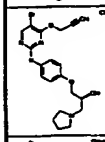
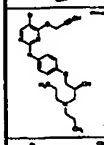
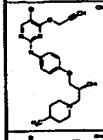
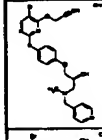
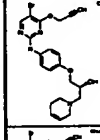
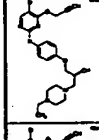
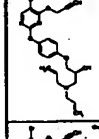
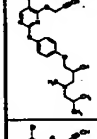
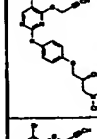
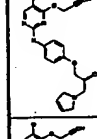
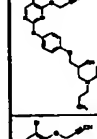
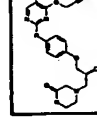














Fig. 7/2

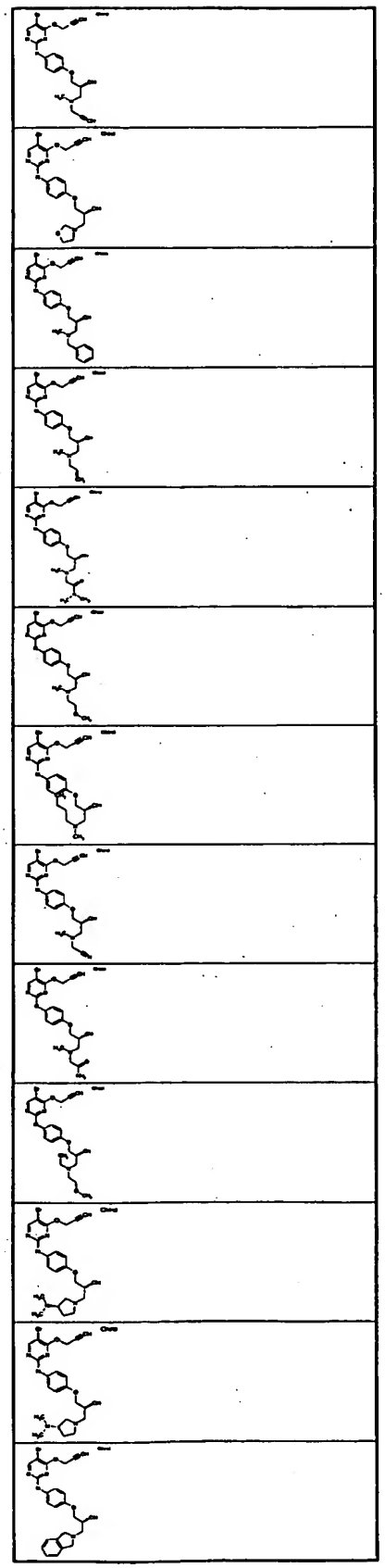


Fig. 7/3

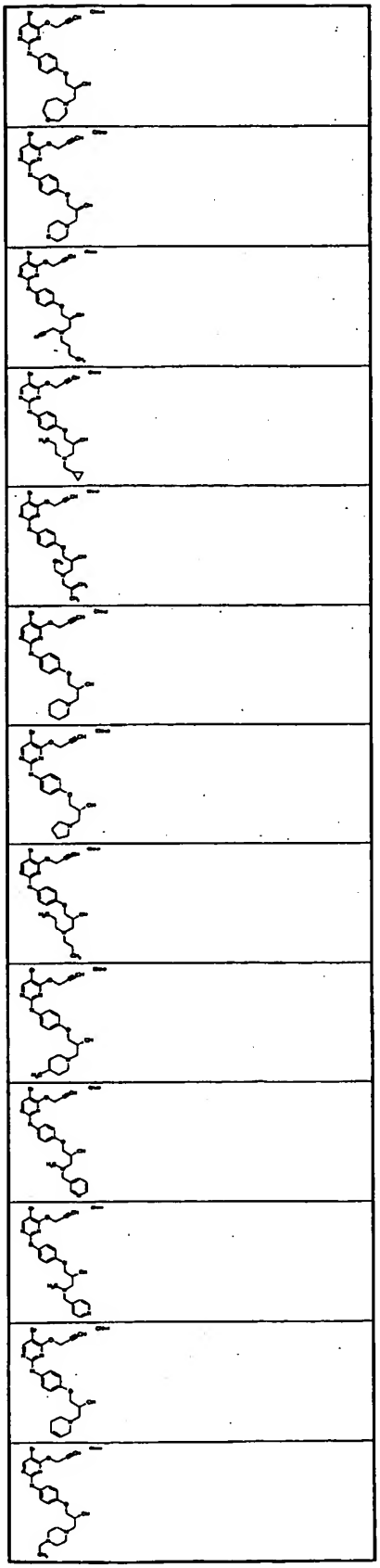


Fig. 7/4

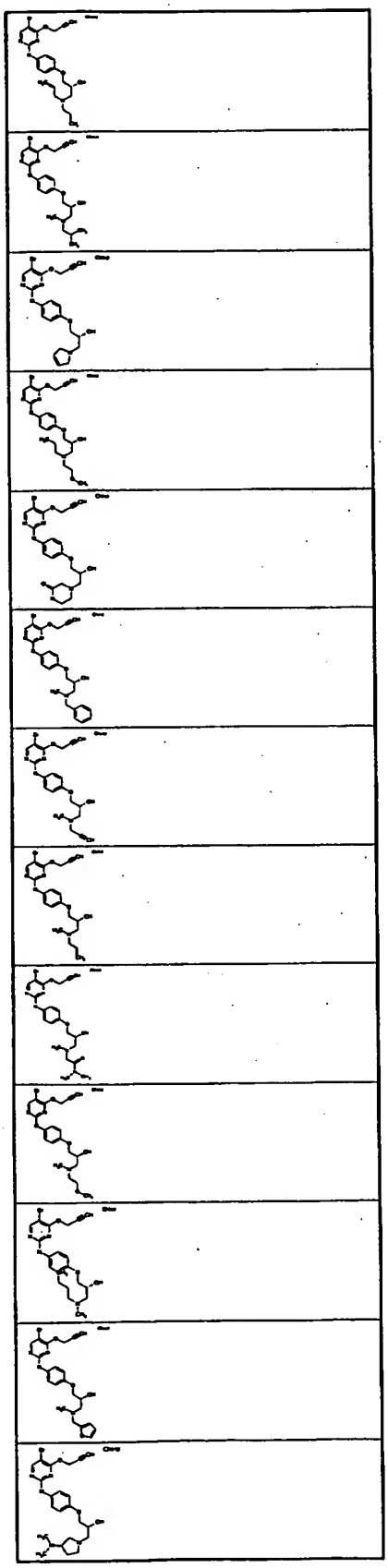


Fig. 7/5

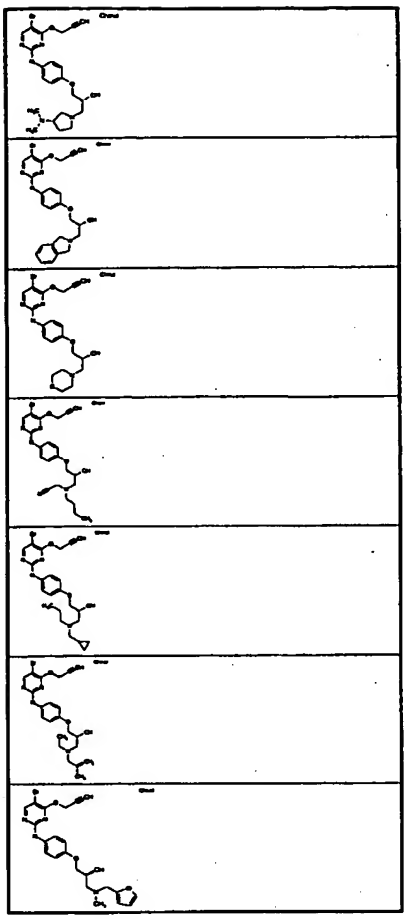


Figure 8

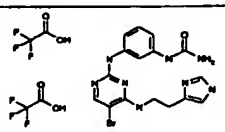
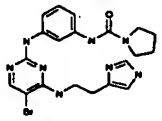
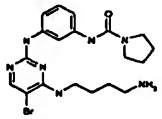
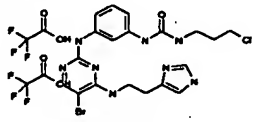
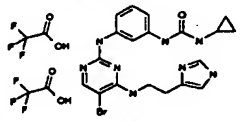
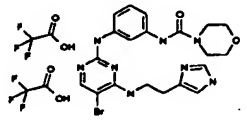
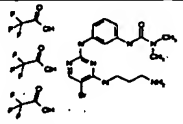
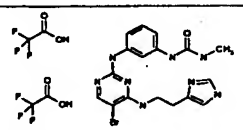
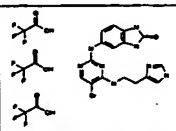
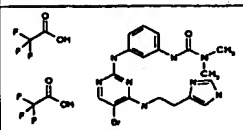
	MOLSTRUCTURE
	
	
	
	
	
	
	
	
	
	

Fig. 9/1

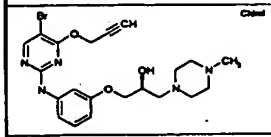
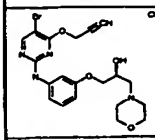
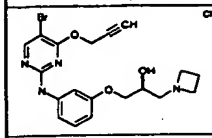
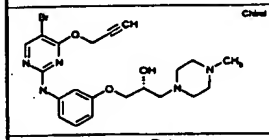
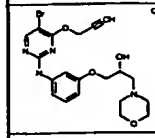
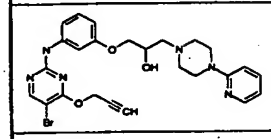
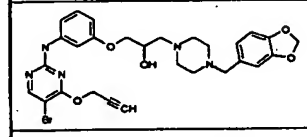
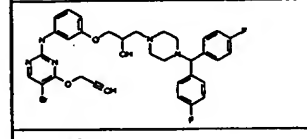
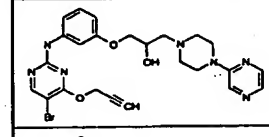
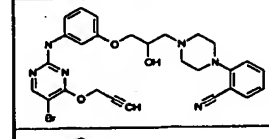
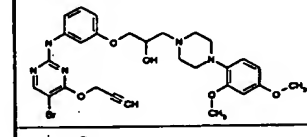
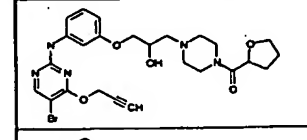
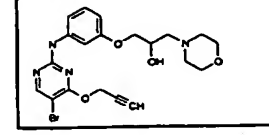
MOLSTRUCTURE














Fig. 9/2

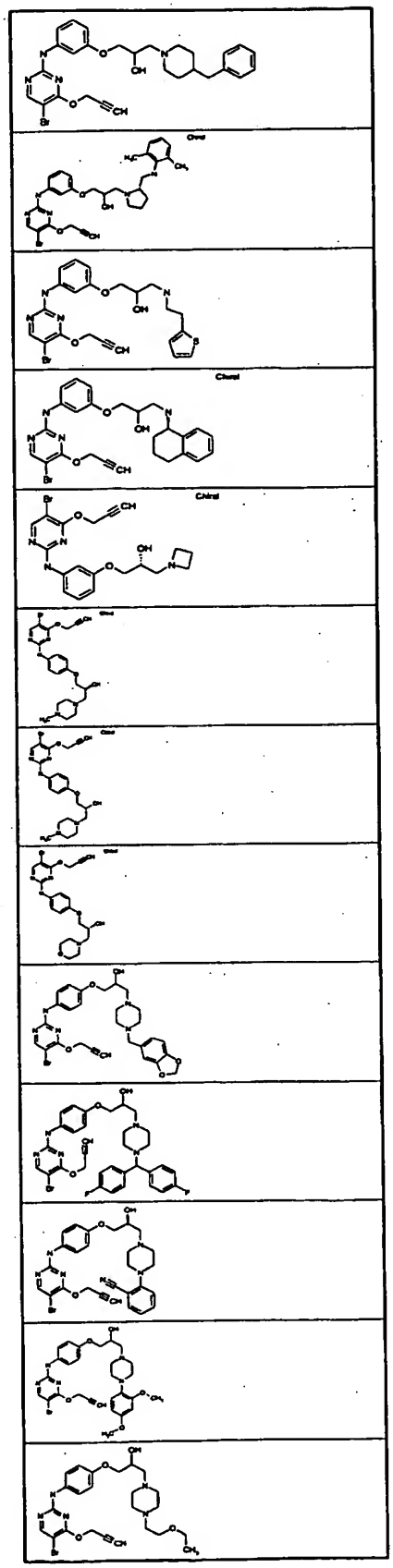


Fig. 9/3